Review

CXCR3-Expressing T Cells in Infections and Autoimmunity

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Abstract

The chemokine receptor CXCR3 and its ligands (MIG/CXCL9, IP-10/CXCL10, and I-TAC/CXCL11) play a central role in the generation of cellular inflammation, both in the protective responses to invading pathogens, and in different pathological conditions associated with autoimmunity. It is worth noting that CXCR3 is highly expressed on innate and adaptive lymphocytes, as well as on various cell subsets that are localized in non-immune organs and tissues. Our review focuses exclusively on CXCR3-expressing T cells, including Th1, Th17.1, Tfh17, Tfh17.1, CXCR3^{+} Treg cells, and Tc1 CD8^{+} T cells. Currently, numerous studies have highlighted the role of CXCR3-dependent interactions in the coordination of inflammation in the peripheral tissues, both to increase recruitment of CD4^{+} and CD8^{+} T cells that upregulate inflammation, and also for recruitment of CXCR3^{+} T regulatory cells to dampen overexuberant responses. Understanding the role of CXCR3 and its ligands might help to apply them as new and effective therapeutic targets in a wide range of diseases.

Keywords: CXCR3 receptor; CXCR3 chemokines; Th1 cells; Th17.1 cells; follicular Th cell subsets; CXCR3^{+} Treg; Tc1; infection; COVID-19; autoimmunity

1. Introduction

In 1996, the human chemokine receptor CXCR3 was discovered [1]. Two years later, the relevant gene was found on chromosome *Xq13.1* [2]. The CXCR3 receptor is a G-protein-coupled receptor (GPCR)-family serpentine transmembrane protein classified as a CXC-type receptor based on the structure of its cognate ligands. This receptor was initially discovered on activated T cells selectively binding ELR-negative CXC chemokines CXCL9 and CXCL10 [1]. It was found that the percentage of CXCR3-expressing T cells exposed *in vitro* to Interleukin (IL)-2 and phytohemagglutinin increased by up to 95% [2]. Accordingly, T cell activation promotes CXCR3 ligand sensitivity. It was revealed that the transcription factor T-bet driving differentiation of 'naïve' T cells into Th1 and cytotoxic CD8^{+} T cells directly promotes the expression of CXCR3 [3–5]. In addition, transcription factor T-bet induces Interferon (IFN)γ secretion and CXCR3 expression on various CD3^{+} cell subsets, including regulatory T cells (Tregs) and follicular T helper (Tfh) cells [6,7]. Later, it was shown that CXCR3 is also observed on the $\gamma\delta$ T cell subset, B cells, natural killer (NK) cells, natural killer T (NKT) cells, and dendritic cells [8–10]. Apart from this, CXCR3 expression was detected on diverse cell types, such as fibroblasts, endothelial, and epithelial cells, as well as astrocytes and smooth muscle cells [8]. Of note, CXCR3 was also de-

scribed in eosinophils and neutrophils involved in inflammatory responses [11,12]. Thus, CXCR3 is expressed on a wide range of immune cells involved in all three types of inflammatory reactions as well as in developing antigen-specific humoral immunity.

After two more alternative splice variants *CXCR3B* and *CXCR3-alt* of the *CXCR3* gene were discovered, CXCR3 receptor was named CXCR3A. CXCR3A consisting of 368 amino acids is the most common form that interacts with cognate ligands CXCL9, CXCL10 and CXCL11 to trigger chemotaxis and intracellular calcium mobilization. CXCL11 and CXCL10 induce activation of the inhibitory Gα subunits (Gαi), activation of β-arrestin 1 and β-arrestin 2 as well as extracellular signal-regulated kinase (ERK)1/2 phosphorylation [13]. Most cells including leukocytes express mainly CXCR3A variant encoded by two exons and separated by one intron that becomes coupled to the Gαi subunit to transduce pro-migration and proliferative signals and elevate level of intracellular calcium [1,2]. While CXCR3B possibly interacts with Gs protein when activated, there is an increase of cyclic adenosine monophosphate (cAMP) within the cell. This leads to induction of p21 transcription, causing apoptosis [14]. CXCR3B consists of 415 amino acid residues, the product of alternative splicing at the 5′ end of the second exon, containing a unique 51 amino acid-long N-terminal tail

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that replaces the four CXCR3A N-terminal residues. Most CXCR3A-positive cells also show low CXCR3B expression.

Existence of two distinct CXCR3 variants potentially exerting opposing effects may account for angiostatic effect assigned to CXCR3 ligands. Moreover, a third alternative splice variant for CXCR3 was identified that results from exon skipping and called CXCR3-alt [15]. CXCR3-alt consists of 267 amino acids, showing marked structural and functional differences, containing only four or five transmembrane domains, however, this receptor variant, like CXCR3A, interacts with Gi-protein. Interestingly, CXCR3-alt isoform is able to bind solely CXCL11 to trigger moderately elevated intracellular calcium level and chemotaxis [16].

CXCR3 ligands exhibit diverse biological effects by acting on various CXCR3-expressing cell types [17]. The presence or absence of the Glu-Leu-Arg (ELR) motif before the first cysteine residue within the amino acid composition of CXC chemokines accounts for downstream potential to stimulate or inhibit angiogenesis. CXCR3-binding CXC chemokines bear no the ELR motif and act, therefore, as angiogenesis inhibitors [18]. Thus, CXCR3 ligands comprise a distinct group of angiostatic chemokines. Among them, two subgroups can be described: (i) key CXCR3 ligands – IFNγ-induced chemokines CXCL9, CXCL10 and CXCL11, (ii) platelet-secreted chemokines – CXCL4 and CXCL4L1 assigned to a separate pair of CXCR3 ligands [19]. In addition, most CXCR3 ligands are able to bind to some glycosaminoglycans (GAGs) found on endothelial cell surface [20–22]. Hence, they compete with diverse angiogenic growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF2) for binding to GAGs and interfere with their binding to cognate receptors [23]. Among the IFNγ-induced CXCR3 agonists, CXCL10 exhibits peak CXCR3B binding affinity [12]. All IFNγ-inducible CXCR3 ligands exhibit higher affinity for the classical receptor CXCR3A than for CXCR3B. Due to the limited number of studies using CXCR3 isoform-specific antibodies, a precise contribution of its splice variants to entire network of IFNγ-dependent CXCR3 ligands in health and disease remains largely obscure. It was shown that various CXCR3 variants and its ligands are found at the site of inflammation, and receptor isoforms may be co-expressed by some cells [14]. This phenomenon poses an additional obstacle to understanding specific *in vivo* contribution of CXCR3 splice variants to interaction with cognate ligands. Thus, CXCR3 is of great interest because each of its three ligands exhibit distinct biological properties and potential to regulate functions of different lineage cells. Moreover, the abundance of different CXCR3-expressing T cell subsets allows to enter the site of inflammation along cognate ligand gradient and participate enabling protective reactions in health and disease.

The most common ligands for CXCR3 include CXCL9, CXCL10, and CXCL11. All three chemokines are encoded on chromosome 4. And their prodiction can be induced by IFNγ [24,25]. However, only CXCL10 and CXCL11 can be produced independently of IFNγ by IFNs type 1 [24–27]. Interestingly, the homology of CXCL11 and CXCR3 is the highest among the three abovementioned ligands [28–30]. Moreover, CXCL11 is one of the most prominent inductors of CXCR3 internalization when contacting CXCR3$^+$ T cells activated by IFNγ in the endothelium [31]. Colvin *et al*. [28] demonstrated that for CXCL11-dependent internalization of CXCR3, the third intracytoplasmatic receptor loop is required. CXCL10 and CXCL9, along with CXCL11, are able to cause CXCR3 internalization. However, unlike CXCL11, another receptor domain is required for internalization. The chemokine receptor CXCR3 is internalized via interactions with CXCL10 and CXCL9 Serine and threonine are present on the carboxile end of the receptor. Internalization is dependent on β-arrestin 1, while CXCL11-dependent internalization requires neither β-arrestin 1 nor the carboxyl-terminal domain of the receptor [28]. Considering the fact that β-arrestin 1 is required for receptor detachment from G-protein, it is possible to presume, that CXCL11 and CXCL9/10 cause the internalization of receptors through different mechanisms. Possibly, CXCL11 itself intitiated the internalization of CXCR3, whereas CXCL9/10 desensitized the receptor with the subsequent dynamin- and clathrin-mediated internalization [32,33]. It is important to highlight the fact that 16 proximal aminoacids of the N-terminal domain of CXCR3 are required for linking with CXCL10, CXCL11, but not CXCL9 [34].

Besides the various domains of CXCR3 required for the functional activity of CXCL9, CXCL10, and CXCL11 individually, there are receptor domains that are required for the functioning of three chemokines combined. For instance, the DRY site in the third transmembrance domain of the CXCR3 receptor is required for CXCL9, CXCL10, and CXCL11-mediated cellular chemotaxis, calcium recruitment, and ERK phosphorylation [28].

The chemokines CXCL10, CXCL0, and CXCL11 can participate in T cell polarization. For instance, CXCL10 and CXCL9 cause expression of T-bet and RORγt transcription factors, which leads to the formation of Th1, Th17 cells, and naïve T lymphocytes [24,35]. CXCL11, however, can inhibit RORγt transcription but not T-bet and induce IL-10 production in CD4$^+$CXCR3$^+$ T cells. The latter may induce naïve T cells to polarize mostly to the Tr1 phenotype [35]. Moreover, CXCL11, while having the highest affinity for CXCR3, can cause internalization of the receptor and make it unreachable for other ligands, therefore contributing to pro-inflammatory cellular repertoire accumulation.

Although all three chemokines are able to chemoattract activated T cells [2], CXCL10, CXCL9, and CXCL11

can contribute to the migration of CXCR3-expressing cells. For instance, $\gamma\delta$T-cells expressing CXCR3 migrate to the inflammation site based on concentrations of CXCL9 [36]. T cells of effector memory mostly react to CXCL11 and have lower sensitivity to CXCL9 or CXCL10 [37].

It is worth mentioning that CXCL10, CXCL9, and CXCL11 have different patterns of expression by various cell types [38]. Flier *et al*. [39] showed differential expression of CXCL10, CXCL9, and CXCL11 in different skin diseases. The authors demonstrated expression of CXCL10 and CXCL11 mostly in basal keratynocytes, whereas expression of CXCL9 was localized mostly in derma infiltrates [39]. Other studies demonstrated that in chronic pulmonary sarcoidosis, alveolar macrophages mostly secreted CXCL10 and not CXCL9 or CXCL11 [40]. CXCL9, however, was associated with the macrophage activation syndrome seen in juvenile rheumatoid arthritis [41]. In some pathologies, the three chemokines are not interchangeable. For instance, in experimental models of dengue fever, the loss of CXCL10 activity was not compensated for by CXCL9 or CXCL11 [42,43].

Therefore, besides obvious similarities, CXCL10, CXCL9, and CXCL11 hold some spatiotemporal and functional differences. Spaciotemporal differences include the production of CXCL10, CXCL9, and CXCL11 by different cells of different localizations at different timespans, depending on the pathological process. Therefore, the abovementioned chemokines cannot substitute for each other in every pathology. Functional differences are caused not only by different types of CXCR3, but also by interactions of CXCL10, CXCL9, and CXCL9 with different receptor domains. The functionality of these chemokines can also depend on CXC3R-expressing cells.

When analyzing CXCR3 surface expression of T helpers, Kim *et al*. [44] found this chemokine receptor expressed on nearly 3% of 'naïve' CD45RA$^+$CD45RO$^-$CD4$^+$ T cells, and on 41.5 $\pm$ 11.2% memory CD45RA$^+$CD45RO$^+$CD4$^+$ T cells in peripheral blood. Similar findings were demonstrated by Rivino *et al*. [45]: out of central memory (CM) Th cells, around 17 $\pm$ 8% cells have phenotype CXCR5$^-$CXCR3$^+$CCR4$^-$. We demonstrated, that among 'naïve' T helper cells (CD45RA$^+$CD62L$^+$) only 3.91 $\pm$ 0.34% cells had CXCR5$^-$CXCR3$^+$CCR6$^-$CCR4$^-$ phenotype. However, as T helpers differentiated into CM (CD45RA$^-$CD62L$^+$), effector memory (EM) (CD45RA$^-$CD62L$^-$) and terminally differentiated effector memory T cell (TEMRA) (CD45RA$^+$CD2L$^-$), an increase of CXCR5$^-$CXCR3$^+$CCR6$^-$CCR4$^-$ Th cells percentage was noted up to 13.73 $\pm$ 0.54%, 22.37 $\pm$ 1.69% and 40.07 $\pm$ 2.77%, respectively [46].

CXCR3$^+$ comprise around 50–90% of CD8$^+$ T cells [47–50]. Our own data has shown that among naïve CD8$^+$ T cells, CXCR3$^+$ percentage comprised 80.67 $\pm$ 1.01%, among CM CD8$^+$ T cells – 86.02 $\pm$ 1.17%, EM CD8$^+$ T cells – 83.46 $\pm$ 1.38%, and within TEMRA CD8$^+$ T cells – 69.55 $\pm$ 1.71% [49].

A decrease in CXCR3$^+$ cells when transitioning into mature effector cells was described by Brainard *et al*. [47]. Besides circulating CM, EM and TEMRA T cells, CXCR3 expression can be found in tissue-resident memory cells (tissue-resident memory (TRM), CD69$^+$CD103$^+$), a special population of T cells that permanently resides in peripheral tissues (e.g., lungs, skin, intestine, etc.) [51], and such positioning at the site of inflammation allows for them to rapidly respond to invading pathogens, as has been recently shown in *M. tuberculosis* infection [52].

As for CXCR3 expression on naïve T cells, it can be associated with stem-like memory T cells (TSCM) in circulation [53]. In murine models, CD8$^+$ T cell transplant to secondary recipient was followed by increased development of graft vs host-like reactions. Murine TSCM phenotype was described as CD44^{low}CD62L^{high}, which matched surface markers of naïve murine T cells. However, surface antigens included Sca-1 molecule (stem cell antigen-1), usually seen on stem cells. Besides, these cells showed high levels of B cell lymphoma 2 (BCL-2) expression, and expressed surface receptor CXCR3. Subsequent studies showed a similar T cell population in the peripherial human blood; it held CD45RO$^-$CCD7$^+$CD45RA$^+$CD62L$^+$CD27$^+$CD28$^+$CD127$^+$ phenotype, usually seen in naïve cells, but they also had surface CD95, CD122, CXC3, and Lymphocyte function-associated antigen 1 (LFA-1) [54].

Fig. 1 demonstrates the chemoattraction of CXCR3$^+$CD4$^+$, and CXCR3$^+$CD8$^+$ T cells. Th1, Th17.1, Tc1, and Tr1 are able to migrate into the inflammatory site based on concentrations of CXCL9, CXCL10, and CXCL11, where, after interacting with antigen-presenting cells (APCs) and inflamed tissue cells, they provide their effector functions.

The studies mentioned above highlighted a crucial role played by CXCR3 in migration of Th1 and Tc1 CD8$^+$ T cells to the site of inflammation in peripheral tissues during type 1 reactions as well as underlie a feedback loop mediated by lymphocyte produced IFNγ and IFNγ-induced CXCR3 ligands released in inflamed tissue (Fig. 1). However, describing novel CXCR3-expressing T cell subsets such as Th17.1, 'double-positive' DP Th17, Tfh1, Tfh17.1, and CXCR3$^+$ Tregs unveiled that mechanisms underlying CXCR3 ligand-mediated responses are multilayered and remain poorly understood. Hence, here we pay special attention to analyzing dynamics of various CXCR3-expressing T cell subsets during autoimmune and infectious pathological processes.
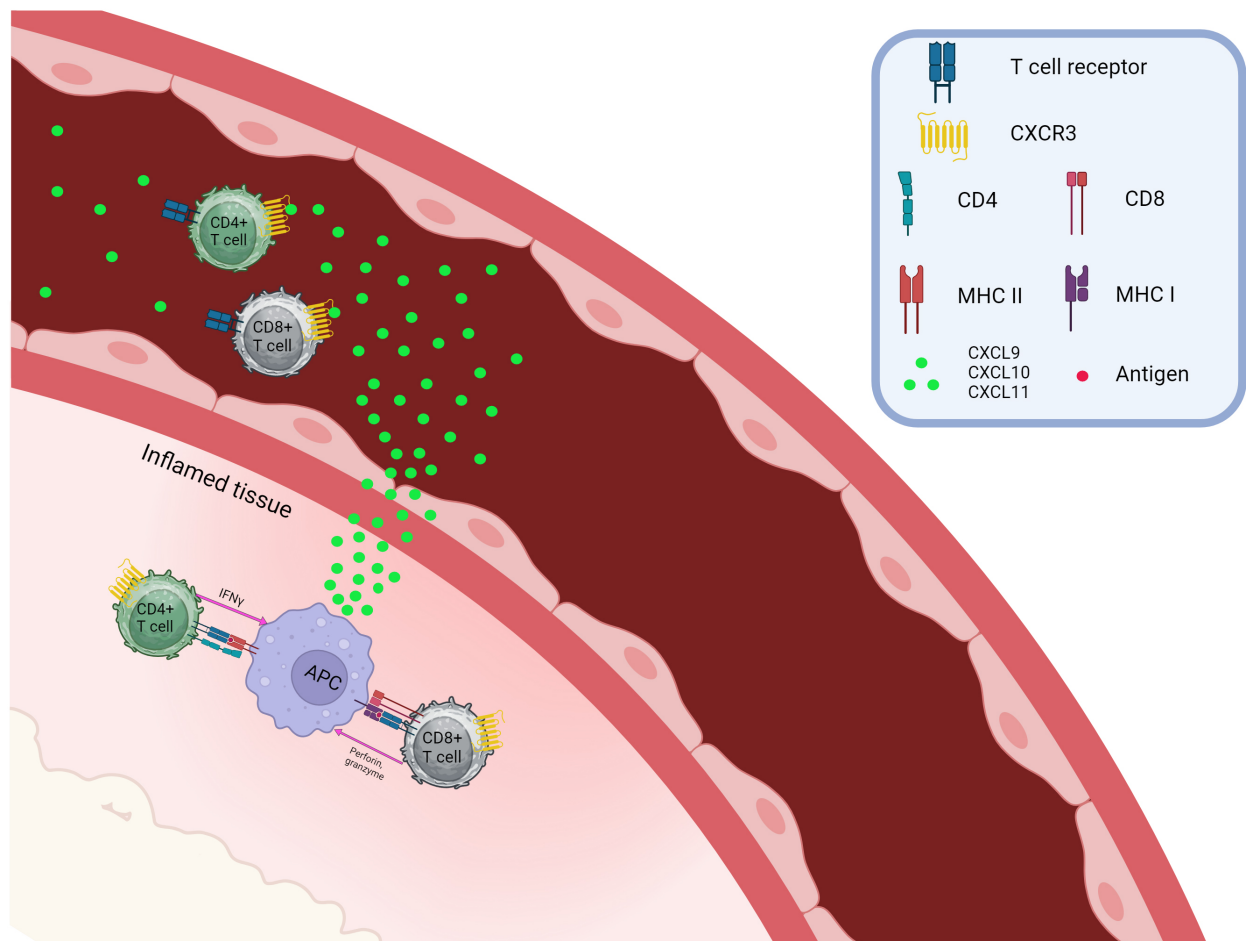
Fig. 1. Chemotaxis of CXCR3-positive T cells. CXCR, C-X-C chemokine receptor; CXCL, C-X-C Ligand; CD, Cluster of Differentiation; APC, Antigen presenting cell; MHC, major histocompatibility complex. Created with BioRender.com.

2. CXCR3 Ligands in Infections and Autoimmunity

In the absence of pro-inflammatory signals, the key CXCR3 ligands CXCL9, CXCL10, and CXCL11 are found at very low levels in the bloodstream and peripheral tissues. At the initial stage of the inflammatory process, their levels increase in the inflammation site, so that IFNγ alone or together with type I interferons triggers the production of CXCL9 as well as CXCL10 and CXCL11, respectively [24]. In inflamed tissues, a rise in the levels of CXCL9, CXCL10, and CXCL11 is accompanied by the migration of CXCR3$^+$ T cells to the site of inflammation and the launch of an effector immune response, which, normally, should result in pathogen elimination. However, a trigger eliciting inflammation agent during autoimmune reactions and chronic infections may not be fully eradicated, thereby, acute inflammation transforms to chronic inflammatory reactions (Table 1, Ref. [39,55–93]). Moreover, it is paralleled with enhanced chemokine production caused by tissue-infiltrating antigen-specific T cells, which leads to increased levels of pro-inflammatory factors not only locally but also at the systemic level.

2.1 CXCR3 Ligands in Infections

High serum levels for all three CXCR3 ligands were observed in tuberculosis (TB) [55], so that for CXCL9, it correlated with systemic organ involvement, whereas CXCL10 levels strongly correlated with respiratory outcomes [94,95]. During *M. tuberculosis* infection, high levels of CXCL9 and CXCL10 were observed in active pulmonary and latent TB infections [96], whereas effective therapy was paralleled with lowered levels of CXCL9 and CXCL10 [97].

A high serum CXCL10 level was strongly associated with severe COVID-19 [56–58]. Moreover, COVID-19 patients with abruptly elevated serum CXCL9 and CXCL10 levels are more likely to result in an unfavorable outcome compared to patients with severe and mild COVID-19 [59]. Finally, computer tomography-verified pneumonia lung injury positively correlated with CXCL10 level [98]. Along with this, elevated levels for all three CXCR3 ligands were found in serum and bronchoalveolar lavage fluid (BALF) samples collected from patients with acute COVID-19 [60,61].

Table 1. Chemokins levels in infections and autoimmunity.

	CXCL9	CXCL10	CXCL11	References
TB	↑	↑	↑	[55]
COVID-19	↑	↑	↑	[56–61]
HIV		↑		[62]
HCV	↑	↑	↑	[63,64]
MS (blood)		↑	↑	[68,69]
MS (liquor)	↑	↑		[65–68]
RA (blood)	↑	↑		[70,71]
RA (synovial fluid)	↑	↑		[72,73]
T1D	↑	↑	↑	[74–77]
SLE	↓	↑	↑	[78–81]
pSS	↑	↑		[82,83]
AS	↑	↑		[84,85]
IBD	↑	↑	↑	[86,87]
Sarcoidosis (blood and BALF)	↑	↑	↑	[88–90]
Psoriasis (blood and skin)	↑	↑	↑	[39,91]
Graves' disease		↑		[92,93]

TB, tuberculosis; HIV, human immunodeficiency virus; HCV, hepatitis C virus; MS, multiple sclerosis; RA, rheumatoid arthritis; T1D, type 1 diabetes; SLE, systemic lupus erythematosus; pSS, Primary Sjögren's syndrome; AS, ankylosing spondylitis; IBD, inflammatory bowel disease; BALF, bronchoalveolar lavage fluid; ↓ indicates decreased levels of circulating cells, ↑ signifies increased levels.

Human immunodeficiency virus (HIV) infection during antiretroviral therapy (ART) was associated with a consistently high CXCL10 level being an important predictor of low therapeutic effectiveness [62], and, in contrast to CD4$^+$ T cell level or viral load, CXCL10 concentration serves as an earlier predictor of disease progression [99]. Moreover, the levels of all three chemokines CXCL9, CXCL10, and CXCL11 inversely correlated with those of 'naïve' circulating CD4$^+$ and CD8$^+$ T cells but positively correlated with the level of peripheral blood Human Leukocyte Antigen (HLA)$^-$DR$^+$CD38$^+$CD4$^+$ T cells, whereas increased CXCL9 and CXCL11 levels were closely associated with higher viral load. Also, plasma levels of CXCL9, CXCL10, and CXCL11 in primary HIV-1 infection served as crucial markers for the long-term prognosis of HIV disease [100].

Plasma CXCL10 levels were significantly higher in hepatitis C virus (HCV)-infected patients with advanced fibrosis, which were also strongly associated with extrahepatic manifestations, including active vasculitis in HCV-associated cryoglobulinemia and autoimmune thyroiditis [63]. It should also be highlighted that CXCL10 level is positively correlated with liver fibrosis score and liver enzyme concentration [101]. Moreover, baseline serum concentrations of CXCL9, CXCL10, and CXCL11 were higher in HCV infection compared to the control group, with a peak level observed for CXCL10, but after successful therapy, those for CXCL10 and CXCL9 decreased significantly, whereas for CXCL11 they remained elevated [64]. A study by Arsent'eva *et al.* [102] also noted increased serum levels of CXCL9/Monokine induced gamma interferon (MIG), CXCL10/Interferon gamma-induced protein (IP)-10, and CXCL11/ITAC in chronic HCV infection, whereas liver biopsies contained higher CXCL10 mRNA levels closely associated with developing fibrosis.

2.2 CXCR3 Ligands in Autoimmunity

A rise in the level of cerebrospinal fluid (CSF) CXCR3 ligands in patients with multiple sclerosis (MS) may be closely related to the recruitment of CXCR3$^+$ T cells from peripheral blood into the nervous tissue, which plays an important role in developing inflammation and the formation of tertiary lymphoid strictures in the central nervous system (CNS). For instance, an increased level of CSF CXCL9 was noted in multiple sclerosis compared to the control group [65]. Moreover, serum CXCL9 levels were correlated with clinical parameters such as the number and volume of brain and spinal cord lesions [66]. Patients with relapsing-remitting multiple sclerosis (RRMS) *vs.* secondary progressive multiple sclerosis (SPMS) were found to have an increased concentration of CSF CXCL10 that also correlated with CXCR3$^+$ T helper cell level [67]. It was also shown that IP-10 concentration was elevated in both serum and CSF in RRMS and SPMS but not in primary progressive multiple sclerosis (PPMS) [68]. A rise in serum CXCL11 level was noted in relapsing-remitting MS compared to the control group [69], although another study found that it remained unaltered [103].

Patients with early-onset and long-term rheumatoid arthritis (RA) *vs.* control group had elevated serum CXCL9 and CXCL10 levels [70,71], which decreased during ef-

fective therapy [70,104]. Importantly, CXCL10 level was tightly related to RA clinical picture and correlated with multiple disease activity measures, including Disease Activity Score in 28 joints (DAS28), Clinical Disease Activity Index (CDAI), swollen joint counts (SJC), tender joint counts (TJC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) [71]. In turn, higher level of multiple chemokines regulating various aspects of cell functioning at the site of inflammation was noted in the synovial fluid [5,105,106]. In particular, levels of synovial fluid (SF) CXCL9 and CXCL10 were also increased in RA [72,73,107], exceeding those for serum counterparts [108]. The data on CXCL11 are quite controversial. For example, Ueno *et al.* [73] showed that serum and SF CXCL11 levels differed insignificantly [94], whereas Aldridge *et al.* [108] found lower SF *vs.* serum CXCL11 (I-TAC) level.

Patients with type 1 diabetes (T1D) showed elevated serum CXCL10 levels [74], whereas in another study, CXCL9 levels, rather than CXCL10 [75] levels, decreased. Increased CXCL9 concentration was also confirmed in the work of Hakimizadeh *et al.* [76]. Powell *et al.* [77] observed elevated levels of CXCL10 and CXCL11 in newly diagnosed individuals and those with long-standing diabetes compared to the control group, whereas CXCL9 levels showed no statistical differences between groups.

Patients with systemic lupus erythematosus (SLE) had a lowered CXCL9 level that correlated with the SLE disease activity index (SLEDAI) score, while atorvastatin therapy was associated with a progressive serum decline for CXCL9 [78]. Along with this, a high plasma CXCL10 level was observed in SLE that additionally correlated with disease activity, anti-DNA antibody level, and SLEDAI score [79,80]. Furthermore, serum CXCL11 levels in SLE patients also exceeded those in the control group but decreased during Tumor Necrosis Factor (TNF)α blocker therapy [81]. Interestingly, SLE patients with pulmonary manifestations had a positive correlation between bronchoalveolar lavage fluid (BALF) CXCL11 level and SLEDAI, as well as BALF CXCL11 concentration and neutrophil count [109].

Sjogren's syndrome (SS) was associated with a higher serum CXCL9 level compared to the control range and was correlated with IgG concentration as well as the European Alliance of Associations for Rheumatology (EULAR) Sjogren's Syndrome Disease Activity Index (ESSDAI) score [82]. In addition, elevated serum CXCL10 levels were also associated with disease activity [83]. However, the serum CXCL11 level was unchanged; it correlated with that of CXCL9 and CXCL10 [110]. Apart from this, it was uncovered that during inflammation, CXCL9, CXCL10, and CXCL11 were produced in tear fluid, also involving corneal and conjunctival epithelium in dry eye syndrome [111]. Noticeably, CXCL11 level correlated with various parameters of the lacrimal film and eye surface, such as basal tear secretion, tear clearance rate, keratoepitheliopathy score, and goblet cell density.

In patients with ankylosing spondylitis (AS) *vs.* the control group, serum CXCL9 levels were found to rise [84]. Moreover, it was also noted that newly diagnosed AS patients contained higher CXCL10 concentrations that correlated with Erythrocyte Sedimentation Rate (ESR), CRP, and the Ankylosing Spondylitis Disease Activity Score (ASDAS), whereas therapy applied decreased CXCL10 levels [85]. However, some studies reported that AS patients had serum CXCL11 levels unchanged [112]. Patients with inflammatory bowel disease (IBD), both Crohn's disease and ulcerative colitis, were found to have higher level for all three chemokines CXCL9, CXCL10 and CXCL11 [86,87] that was further corroborated in animal model [87].

Patients with pulmonary sarcoidosis had increased serum CXCL9 and CXCL10 levels compared to the control group [88]. Moreover, CXCL10 was also accumulated in granulomas, which is believed to mirror its important role in granuloma formation [89]. It was also shown that CXCL9 was stronger correlated with systemic organ involvement, whereas CXCL10 was more predictive for lung outcomes [94]. Also, high levels of all three CXCR3 ligands were observed in BALF samples [90].

Assessing the serum concentration of CXCR3 ligands CXCL9, CXCL10, and CXCL11 in patients with psoriasis is important not only for understanding the disease pathogenesis but also to represent promising targets for evaluating therapeutic effectiveness [113]. For instance, serum CXCL9 level was increased in psoriasis *vs.* control group [91]. Moreover, elevated CXCL9 expression was associated with a high risk of developing psoriasis [114]. However, opposite results were obtained by Lima *et al.* [115], failing to note a change in CXCL9 and CXCL10 levels and detecting no relation between them and clinical data. *In situ* production of CXCL10 and CXCL11 at the site of inflammation is mainly performed by keratinocytes, whereas CXCL9 is primarily released by dermis-infiltrating cells [39].

CXCR3 ligands play an essential role in the pathogenesis of autoimmune thyroid lesions [116]. CXCL10 levels were increased in newly diagnosed patients with Graves' disease compared to the control group, whereas histology examination revealed that expression of IP-10/CXCL10 and MIG/CXCL9 was predominantly associated with lymphocytes and macrophages infiltrating thyroid gland tissue and resident epithelial follicular cells [92]. Moreover, CXCL10 levels remained elevated even in remission [93].

The majority of the pathological events described above were paralleled with increased levels of CXCR3 ligands in both the serum samples and at the site of inflammation. CXCR3 ligands were produced not only by blood cells infiltrating inflamed tissues, but also by resident tissue cells. Apparently, the initial entry of CXCR3$^+$ T cells into the site of inflammation is accompanied by their activation followed by the by the production of proinflammatory cytokines, including IFNγ, which stimulates surround-

ing cells to release CXCL9, CXCL10, and CXCL11 at a higher level. Low efficiency of pathogen elimination (in infection) or inability to fully remove antigens resulting in T cell activation (in autoimmune processes) elicit reciprocally potentiated functions both in T cells and resident tissue cells. In this case, CXCL9 and CXCL10 exhibit diverse pro-inflammatory effects and may augment the inflammatory process manifold, as suggested by their close relation with clinical manifestations in the vast majority of pathological processes described here, whereas the role of CXCL11 in the underlying pathogenesis potentially able to restrain inflammation remains understudied.

As was previously described, it is CXCR3 ligands that form the microenvironment required for cellular attraction in type I inflammation. Moreover, effective $CXC3^+$ involvement in inflammatory sites will determine the efficacy of pathogen elimination in infectious diseases and autoimmune inflammation. Therefore, one of the main goals of our review was to analyze the functions and dynamics behind $CXCR3^+$ T cells in different populations and how CXC3 ligands make them accumulate and interact during inflammation.

3. CXCR3-Expressing Th1 Cells in Infections and Autoimmunity

Th1 cells are characterized as $CD3^+CD4^+CXCR5^-CXCR3^+CCR6^-CCR4^-$ cells [117] able to secrete IFNγ, TNFα and IL-2. They also express a signature transcription factor T-bet, which promotes production of effector cytokines, primarily IFNγ [3]. IL-12 skews 'naïve' Th0 cell polarization towards Th1 cells by inducing T-bet expression [118], that can be also triggered via an autocrine route acting through surface IFNγ receptor transducing IFNγ-mediated effects [119]. Moreover, Th1 cell polarization was also noted to be contributed by IL-27 believed to upregulate IL-12 receptor on Th0 cells thereby enhancing sensitivity to the relevant polarizing cytokine [120]. In turn, activated T-bet promotes CXCR3 expression, which is primarily involved in the recruitment of effector Th1 cells to the site of inflammation [121]. Migration is facilitated by CXCR3 receptor ligands (CXCL9, CXCL10, and CXCL11) initially produced by various cells in the inflamed tissue. After migration to the site of inflammation, Th1 cells interacting with antigen-presenting cells begin to secrete diverse cytokines, primarily IFNγ, exerting proinflammatory effects [122], such as the induced production of CXCR3 ligands acting via STAT transcription factors [123]. IFNγ-induced CXCL9, CXCL10, and CXCL11 in inflamed tissues also recruit effector cytotoxic $CD8^+$ T cells (CTLs) into the site of inflammation [124]. Further, Th1 cell-produced IFNγ promotes M0-to-M1 macrophage polarization [125]. M1 macrophages and Th1 cells are the major players underlying delayed-type hypersensitivity reactions [126].

Thus, Th1 cells are collectively characterized by cell surface CD4 and CXCR3 markers as well as cytosolic T-bet transcription factor and IFNγ-bearing granules.

3.1 Th1 Cells in Infections

Plasmacytoid dendritic cells (pDC) and conventional dendritic cells (cDC1), IL-12, and IFNγ necessary for innate lymphoid cells type 1 (ILC1) activation and Th0-to-Th1 "polarization" play an important role in the initiation of an antigen-specific type 1 immune response (directed against intracellular pathogens, primarily viruses and bacteria) [127]. Th1 cells are involved in enabling adaptive immunity-related cellular reactions via production of pro-inflammatory cytokines IFNγ and TNFα, cytotoxic cells, and cytokines (IL-2 and IL-15) targeting tissue M1 macrophages.

It was observed that the N- and S-proteins of Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) stimulated the production of IFNγ and IL-2 by T helper 1 cells, and also triggered the proliferation of Th1 cells [128], which are capable of migrating to the site of inflammation. Nevertheless, the involvement of Th1 cells in the development of COVID-19 is still a subject of debate. Some studies indicate that Th1 cells expressing IFNγ have a beneficial impact, and their increased activity is linked to a less severe progression of the disease [129]. On the other hand, older patients with typically severe COVID-19 had decreased level of IFNγ-producing virus-specific Th1 cells, which also indirectly indicates crucial role of these cells in developing effective immune response [130]. Th1 cell migration into inflamed tissues is indirectly evidenced by a mildly lowered proportion of such a peripheral blood total pool in patients with acute COVID-19, as also noted in several independent studies [131,132]. In this regard, Wang et al. [133] revealed elevated $CD4^+CXCR3^+$ T cell level on colonic biopsies from patients with COVID-19-related intestinal lesions, whereas He et al. [134] showed similar data in BALF from patients with COVID-19 pneumonia. Gong et al. [135] also found that a more severe illness progression was associated with a decline in the number of Th1 cells, which had reduced activation due to decreased expression of CD38 and HLA-DR. Additional research has revealed that Th1 cells play a pathogenic function by producing excessive amounts of pro-inflammatory cytokines, such as IFNγ and TNFα. This leads to a condition known as "cytokine storm" and acute respiratory distress syndrome (ARDS) [136–138]. Thus, Th1 cells play an important role in protecting the host from acute respiratory viral infections. However, COVID-19-related Th1 cell hyperactivation contributes to impaired maturation of these cells, subsequently potentiating low-grade inflammation resulting in disease aggravation.

Patients with active pulmonary TB were shown to have increased level of peripheral blood $CD4^+CXCR3^{hi}$ cells able to rapidly secrete cytokines in response to diverse

M. tuberculosis antigens [139]. M. Tuberculosis (MTB)-specific Th1 cells might be able to migrate into foci of infection. Nikitina *et al*. [140] noticed that dominant lung CD4$^+$ T cells in active pulmonary tuberculosis mimicked CXCR3$^+$CCR6$^-$ population. On the other hand, highly expressed CXCR3 and its cognate ligands CXCL9, CXCL10, CXCL11 were also demonstrated in tuberculosis granuloma [141,142]. Moreover, increased CXCR3$^+$ central memory (CM) and CXCR3$^+$ EM T cell levels were observed in BALF *vs.* peripheral blood paired samples from TB patients [143]. Hence, Th1 cells in TB contribute to granuloma formation and restrain spreading of infectious process.

Chemokine receptor CXCR3 and its IP-10 ligand are considered as markers to assess the size of the HIV cell reservoir [144,145]. CXCR3 and IP-10 are more often found in gut-associated lymphoid tissue (GALT) than in peripheral blood in chronically simian immunodeficiency virus (SIV)-infected primates, CXCR3 and IP-10 are more often found in GALT than in peripheral blood [145] that was related to HIV reservoir size. CXCR3 is predominantly expressed in Th1 cells that together with CCR6 defines a CD4$^+$ T-cell subset mainly enriched with HIV DNA in ART-treated HIV-infected subjects [146]. Serum IP-10 level in HIV-positive patients is increased while CXCR3 becomes activated in memory CD4$^+$ T cells [147,148]. In particular, chemokines such as IP-10 acting on resting CD4$^+$ T cells ensure effective HIV-1 nuclear localization and HIV-1 provirus integration [149]. Thus, CXCR3/IP-10 axis can stimulate HIV-1 replication in periphery and mucous membranes and, therefore, chronic activation of host immunity. In addition, the HIV replication-competent viruses were mainly found in peripheral blood CXCR3-expressing CD4$^+$ T cells in HIV$^+$ patients [150], whereas serum IP-10 level correlate with blood and semen virus reservoir size [145,151]. CXCR3 and IP-10 stimulating the HIV-targeted T cells to migrate into the focus of inflammation in peripheral tissues are abundantly produced in the small intestine and stimulate HIV replication *in vitro* [146]. Moreover, it was shown that CXCR3/IP-10-blocking monoclonal antibody lowers *in vitro* HIV-1 replication. Furthermore, Augustin *et al*. [152] assessed a role for CXCR3 and IP-10 in GALT in HIV-infected individuals. Although a percentage of peripheral blood CD4$^+$ T cells was similar in peripheral blood, terminal ileum and rectum, HIV and CXCR3 DNA expression was markedly elevated, whereas IP-10 level was downmodulated in the ilium compared to serum samples. No significant correlation between CXCR3 expression and memory CD4$^+$ T cell subsets, IP-10 and HIV DNA levels measured in the blood, terminal ilium and rectum was observed. Thus, neither CXCR3 nor IP-10 level in chronic HIV-1 infection point at GALT HIV reservoir size [152].

Patients with HCV were found to have elevated CD3$^+$CD4$^+$CXCR3$^+$ and CD3$^+$CD4$^+$CCR6$^+$ Th cell levels, particularly showing that the percentage of CXCR3$^+$ Th cells (CD3$^+$CD4$^+$CXCR3$^+$) was increased, although it was solely observed for CD3$^+$CD4$^+$CXCR3$^+$CCR6$^+$ cells [153]. Furthermore, the majority of liver-derived T cells expressed CXCR3 chemokine receptors, representing high enrichment over levels of CXCR3$^+$ T cells in blood from patients with HCV [154].

3.2 Th1 Cells in Autoimmunity

Th1 cells exert multifaceted effects in development of autoimmune diseases. In this regard, Th1 cells may trigger induction of inflammation or antagonize autoreactive cells in a context-dependent manner. Autoreactive Th1 cells are considered as the major T cell subset promoting development of autoimmune inflammation in a wide range of autoimmune disease before Th17 and Th17.1 cells were identified.

In multiple sclerosis, Th1 cell function remains controversial because some studies report that these cells migrate across the blood-brain barrier (BBB) and participate in developing autoimmune inflammation [155,156], whereas others demonstrate that they provide immunosurveillance, but Th17.1 cells display an autoimmune phenotype [157]. Taking into consideration recent discoveries in the autoimmune mechanism of multiple sclerosis, it may be concluded that it is Th17.1 cells that are mainly involved in this pathology. However, studies conducted in the 2000s suggested a role for the CXCR3 receptor in T cell migration across the BBB [156,158,159]. Hence, it implies that CXCR3-positive Th1 cells may enter brain tissue and maintain autoimmune inflammation in multiple sclerosis. Moreover, Sørensen *et al*. [156] demonstrated CXCR3$^+$ T cell accumulation during multiple sclerosis lesion formation, whereas Nakajima *et al*. [160] showed increased cerebrospinal fluid (CSF) CXCR3$^-$ expressing CD4$^+$ T cell level in patients with multiple sclerosis as well as a higher percentage of peripheral blood CD4$^+$CXCR3$^+$ cells in recurrent multiple sclerosis. Thus, despite the fact that Th17.1 cells are crucial to nerve tissue damage in multiple sclerosis, Th1 level may be a prognostic factor for the disease course.

In rheumatoid arthritis, the level of peripheral blood CD4$^+$CXCR3$^+$ T cells was decreased [161], whereas in SF and the synovium it tended to increase [108,161]. The data presented above suggests Th1 migration to affected joints in rheumatoid arthritis. Presumably, IFNγ-producing Th1 cells sustain chronic inflammation in the synovium, being additionally involved in the formation the tertiary lymphoid organs. However, a body of recent studies shows that synovial and synovial fluid T cells bear a CCR6$^+$CXCR3$^+$ phenotype and may simultaneously produce IFNγ and IL-17A [162]. However, such an immunophenotype is typical of Th17.1 cells, thereby allowing us to consider this lymphocyte subset as essential in the development of Rheumatoid arthritis (RA) inflammation. Upon this, identifying the peripheral blood Th1 cell phenotype in rheumatoid arthritis may be useful for assessing therapeutic efficacy and disease

activity. In addition, Aeberli *et al*. [163] demonstrated a higher percentage of peripheral blood CXCR3-expressing CD4$^+$ and CD8$^+$ T cells in infliximab-treated RA patients at weeks 6 and 14. Also, a negative correlation between CD4$^+$CXCR3$^+$ T cell level and the Rheumatoid Arthritis Disease Activity Score (DAS-28) was noted [163].

In type 1 diabetes, peripheral blood Th1 (CD4$^+$CXCR3$^+$) cell levels were decreased if compared to healthy donors [164,165], and their frequencies were affected by the disease's clinical manifestation. In particular, patients with fulminant onset of T1D had decreased CXCR3-expressing CD4$^+$ T cells if compared to typical and healthy subjects, while patients with a typical pattern of T1D onset had significantly higher levels of Th1 cells than healthy controls and patients with fulminant onset of T1D [165]. It is plausible that Th1 cells may migrate into the pancreas and take part in pancreatic beta cell lysis. Uno *et al*. [166] showed that pancreatic beta cells from T1D patients selectively express the CXCL10 ligand for the CXCR3 receptor. Moreover, beta cell-positive regions in the pancreatic islets were infiltrated with CD3$^+$CXCR3$^+$ lymphocytes [166], thereby supporting the hypothesis about selective destruction of pancreatic beta cells. Blahnik *et al*. [167] described beta cell-specific CXCR3$^+$CCR7$^-$ T cells in T1D patients, suggesting a Th1-like effector phenotype. Assessing peripheral blood Th1 cell subset composition in T1D may be prognostic based on the data reported by Aso *et al*. [168], who revealed that T1D duration was positively correlated with IFNγ-producing CXCR3$^+$ T cell levels.

In diffuse connective tissue diseases (DCTDs), the role of Th1 cells was also assessed. For instance, patients with SLE were found to have peripheral blood Th1 and Th17 cell subsets with high IL-21 expression levels, suggesting that they may provide help to B cells [169]. In addition, a rise in CD4$^+$CXCR3$^+$ T cell level was associated with disease severity, showing that active *vs*. remission patients with SLE and healthy subjects had significantly higher levels of CXCR3$^-$ and CCR5$^-$ expressing CD4$^+$ T cells [170,171]. Such a T cell subset plays a role in SLE-related kidney damage, so Enghard *et al*. [172] revealed that around 50% of kidney CD4$^+$ T cells were CXCR3 positive, and CD4$^+$CXCR3$^+$ T cell levels also mirrored lupus nephritis activity.

In the pathogenesis of Sjögren's syndrome, Th1 cells are involved in damaging target organs. In this regard, lung biopsies were noted to be enriched in Th1 cells within the area of fibrosis, whereas in idiopathic pulmonary fibrosis, a similar sign was not observed [173]. In contrast, the level of peripheral blood Th1 cells was decreased in patients with Sjögren's syndrome [174]. In dermatomyositis, musculo-cutaneous flap biopsies showed mononuclear cells predominantly with a CD4$^+$CXCR3$^+$ phenotype, whereas skin biopsies in discoid SLE usually lacked CXCR3$^-$ positive cells [175].

Few studies were aimed at analyzing the role of Th1 cells in the pathogenesis of systemic vasculitis. For instance, Lintermans *et al*. [176] demonstrated a decline in peripheral blood effector memory (EM) Th1 cell level in Wegener's granulomatosis. On the contrary, other studies demonstrated elevated peripheral blood CD4$^+$CXCR3$^+$ T cell percentages in antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis [177]. Hence, a role for Th1 cells in systemic vasculitis remains unclear and requires further exploration.

The percentage of Th1 cells was significantly increased in mild and severe AS compared with control subjects, whereas that of Th2 cells remained affected insignificantly [178]. Moreover, the Th1/Th2 cell ratio was markedly higher in mild and severe ankylosing spondylitis patients. Th17 cell levels were also significantly increased in mild and severe ankylosing spondylitis, whereas inter-group Treg cell percentages did not differ. Therefore, Th17/Treg cells are prominently higher in mild and severe ankylosing spondylitis. Assessing expression for key cytokines typical of "polarized" Th cells revealed a significantly increased level of IFNγ and IL-17A mRNA in circulating cells in mild and severe ankylosing spondylitis compared to the control group, whereas that of IL-4 and TGFβ mRNA found no significant difference between the three groups. Another study reported that the level of peripheral blood CD4$^+$CXCR3$^+$ Th1 cells increased in patients compared to volunteers [179]. Moreover, AS patients were found to have significantly higher peripheral blood CD4$^+$CCR4$^+$ Th2 and CD4$^+$CCR4$^+$CCR6$^+$ Th17 cell levels. Similarly, increased percentages of circulating CCR4$^+$CD4$^+$ T cells in patients with AS *vs*. control subjects were found by Yang *et al*. [180], and CCR4$^+$CD4$^+$ T cell frequencies were correlated with the Bath AS Disease Activity Index (BASDAI) score. Elevated percentages of IFNγ- and TNFα-secreting CD4$^+$ and CD8$^+$ T cells, expressing Th1 and Tc1 cell phenotypes, respectively, were noted both in patients with AS and HLA-B27-positive volunteers compared with HLA-B27-negative control subjects [181].

Patients with Crohn's disease (CD) had decreased peripheral blood CD4$^+$CXCR3$^+$ T cell levels [182]. However, an immunohistochemistry study assessing foci of inflammation showed that this cell type was enriched in the inflamed mucosa of IBD patients. Papadakis *et al*. [183] showed that CXCR3 is expressed on the majority of gut lamina propria CD4$^+$ T cells. An in-depth study analyzing lymphocytic infiltrate in CD intestinal mucosa revealed that CCR6 and CXCR3 were co-expressed on CD4$^+$ T cells [184], allowing to assign them to the Th17.1 phenotype. It is also known that Crohn's disease is characterized by altered immune tolerance to commensal bacteria. For instance, Cook *et al*. [185] assessed the flagellin-specific responses of diverse Th cell subsets isolated from CD patients and found that FliC- and Fla2-specific CD4$^+$ T cells

were dominated by Th17 and Th17.1 rather than Th1 cells. Thus, a key role in emerging granulomatous inflammation in Crohn's disease is related not only to Th1 cells but also to Th17.1 cells.

In pulmonary sarcoidosis, circulating CD4$^+$CXCR3$^+$ T cell levels were significantly decreased compared to healthy controls [186]. Th1 cells are among those essential cells involved in the development of delayed-type hypersensitivity (DTH) reactions and granuloma formation typical for sarcoidosis. Such data suggest that Th1 cells migrate to the site of inflammation. The study by Facco *et al*. [187] showed high infiltration of CD4$^+$CXCR3$^+$ T cells into the lungs during pulmonary sarcoidosis, corroborating our assumption. Also, patients with chronic sarcoidosis had an increased level of BALF CD4$^+$CXCR3$^+$ T cells [188]. After BALF and peripheral blood cells obtained from patients with sarcoidosis and volunteers were stimulated with phorbol ester and ionomycin, types 1 and 2 Th cells and CTL levels were analyzed for cytokine secretion. It was found that Tc1 and Tc2 secretory potentials in both biological materials did not significantly differ between patients and control subjects. In contrast, BALF Th1 cell cytokine production (post-stimulation) was higher in patients with sarcoidosis. On the other hand, while comparing BALF Th1 with Th2 cells collected from volunteers, it was shown that the former was a priori more abundant under normal conditions [189]. Thus, it may be concluded that Th1 cells are involved in emerging granulomatous inflammation during chronic pulmonary sarcoidosis.

Regarding psoriasis, it was revealed that CCR6$^-$CCR4$^+$CXCR3$^+$ memory Th cell levels tend to decline [190]. Similar findings may also mirror partial antigenic stimulation of autoreactive Th1 cell clones. Flier *et al*. [39] CXCR3 was expressed by the majority of psoriasis skin-infiltrating CD4$^+$ and CD8$^+$ T cells, suggesting a functional interplay between locally produced chemokines and CXCR3-expressing T cells. The latter may become recruited into the skin layers upon disease exacerbation. Furthermore, Flier *et al*. [39] showed that CXCR3 was expressed by the majority of psoriasis skin-infiltrating CD4$^+$ and CD8$^+$ T cells, suggesting a functional interplay between locally produced chemokines and CXCR3-expressing T cells. Diani *et al*. [191] also noted that effector CXCR3$^+$CD4$^+$ T cells were selectively recruited to the skin compartment during psoriasis. Furthermore, CXCR3$^+$ T cell accumulation in the joint tissue of patients with psoriatic arthritis was followed by an increase in CXCL10 levels in SF [50].

Patients with coexisting Graves' disease and T1D had decreased peripheral blood Th1 cell levels compared with the control and patient's groups with either disease alone [168]. Moreover, normal thyroid tissue virtually lacked expression of IP-10/CXCL10, MIG/CXCL9, and CXCR3, whereas the onset of the inflammatory process in patients with Graves' disease was paralleled with their abruptly el-

evated level, which may cause Th1 cell infiltration into inflamed tissue [92]. A high CXCL10 level was also observed in active Graves' ophthalmopathy [192]. Elevated serum CXCL9 and CXCL11 levels were also related to active first-onset Graves' disease and recurrent hyperthyroiditis, whereas efficient therapeutic intervention downmodulated their production [192].

Patients with myasthenia gravis *vs*. healthy subjects showed decreased levels of circulating CXCR3$^+$CD4$^+$ T cells as well as inverse correlation between the level of these cells and disease severity according to the MGFA scale, whereas therapeutic intervention gradually restored level of these cells to control range [193].

Therefore, in infections caused by intracellular pathogens (e.g., viruses or *M. tuberculosis*), CXCR3-expressing Th1 cells have an important role in the induction of the infectious process and the activation of effector cells via key cytokine production. At the same time, long-term activation of Th1 cells (increase in expression of activation surface markers, excessive cytokine production, and accumulation of cells in inflammation cytote) is followed by damage to surrounding cells of the host, leading to defects in the functioning of inflamed organs and, potentially, to the progression of autoimmune diseases.

Thus, despite the long-standing discovery of the Th1 cell subset, their role in autoimmune diseases continues to raise questions. In connection with recent research, other cells expressing CXCR3 such as Th17.1 cell subset come to the fore while exploring development of autoimmune granulomatous diseases. The essential role for Th17.1 cell subset was also noted in organ-specific diseases such as multiple sclerosis. However, Th1 cells still play a dominant role among other CXCR3$^+$ T lymphocytes in some autoimmune diseases, e.g., type 1 diabetes.

4. CXCR3-Expressing Th17 Cell Subsets in Infections and Autoimmunity

Th17 cells and the pro-inflammatory cytokines they produce play an essential role in regulating type 3 inflammation [194] aimed at elimination of extracellular bacteria and fungi. Such inflammation is characterized by influx of circulating neutrophils into inflamed tissues as well as activation of barrier tissue cells (primarily mucosal epithelial cells) along with elevated mucus production and antimicrobial factor release [195]. Currently, Th17 cells are divided into several separate subpopulations based on CCR4 and CXCR3 co-expression by distinguishing "classical" CCR4$^+$CXCR3$^-$, "double-positive" CCR4$^+$CXCR3$^+$, "non-classical" Th17.1 CCR4$^-$CXCR3$^+$, as well as "double-negative" CCR4$^-$CXCR3$^-$ cells [196]. "Classical" Th17 cells consist of two major cell types solely bearing surface CCR6 or co-expressing CCR6 and CCR4 markers [197], able to abundantly produce IL-17A in response to stimulation, whereas the remaining cytokines, primarily IL-22 and granulocyte-macrophage colony-

stimulating factor (GM-CSF), they produce at much lower level are less pronounced in them. Proliferative potential of such cells *in vitro* co-cultured with autological Tregs becomes inhibited much less profoundly compared to Th1 and Th2 cells evidencing that they are poorly sensitive to action of anti -inflammatory cytokines [198].

The population of "non-classical" Th17 – Th1/Th17 or Th17.1 – bearing Th1 and Th17 cell features including expression of the nuclear factors TBX21 and RORC and potential to produce IFNγ and IL-17A was thoroughly described recently [196], although for the first time it was noted as early as in 2007 [198]. Compared to "classical" Th17 cells, it exerts high proliferative potential after T cell receptor (TCR)-mediated activation coupled to upregulated expression of transcription factors T-BET, STAT4 and RUNX paralleled with downmodulated AHR level [196]. Moreover, Th17.1 cells secreted high quantity of GM-CSF recruiting and activating neutrophils in the focus of inflammation, whereas IFNγ they produce activated tissue macrophages. It was shown that human peripheral blood "non-classical" Th17 cells featured with CCR6$^+$CXCR3^{hi}CCR4^{lo}CCR10$^-$CD161$^+$ phenotype expressed abundantly MDR1 transporter accounting for cell resistance to diverse various drugs including glucocorticoids [199]. Altogether, it allowed to consider Th17.1 cells as a pathogenic lineage, i.e., contributing to development and maintenance of tissue inflammatory reactions. Such observations were corroborated by molecular biological studies showing that Th17.1 cells bear mRNA for proinflammatory cytokines CCL3, CCL4, CCL5, granzyme B, IL-3, IL-22, GM-CSF, STAT1, T-bet and IL-23R at markedly higher level than in other Th17 cell subsets [200].

Two more new Th17 cell subsets were also characterized: CCR4$^-$CXCR3$^-$ ("double negative" or CCR6$^+$DN) and CCR4$^+$CXCR3$^+$ ("double positive" or CCR6$^+$DP), which fundamentally differed in related functional features from the previously described Th17 cells [201]. For instance, CCR6$^+$DN *vs.* "classical" Th17 cells expressed more IFNγ, IL-17A, IL-17F, MIP-3a/CCL20, and TNFα but had lowered activity of the IL-13-encoding gene. While comparing CCR6$^+$DN Th17 and Th17.1 cells, it was noted that along with increased expression of IL-17A and IL-17F, they were also characterized by lowered potential to produce IFNγ and TNFα, but almost comparable expression levels for GM-CSF, IL-10, and IL-22 were found in all three Th17 cell subsets. Regarding production and secretion of Th17 cytokines *in vitro*, the CCR6$^+$DN Th17 cell subset was found to be a major IL-17F and IL-8 producer compared to Th17 and Th1/Th17 cells. The CCL20 level was moderately higher than that observed for Th17 cells but comparable to that shown in Th17.1 cells, whereas all cell lineages did not differ in IL-22 expression at the protein level. Of note, CCR6$^+$DN differed fundamentally from CCR6$^+$DP Th17 cells in terms of secreting solely IL-17F, IL-22, and CCL20 because the latter cell subset virtually

lacked production of this cytokine panel as well as exerted the lowest potential among all Th17 cell subsets to produce IFNγ, IL-17A, TNFα, and IL-13. Furthermore, CCR6$^+$DN and CCR6$^+$DP Th17 cell subsets profoundly differed in the level of expressed homing molecules [201].

For instance, CCR6$^+$DN Th17 cells were characterized by a high mRNA level for molecules driving migration into lymphoid tissue (CCR7, CXCR5, CXCL13, SELL, SIRP1, JAM3, and AIF1). On the contrary, CCR6$^+$DP Th17 cells expressed mainly adhesion molecules and chemokine receptors necessary for migration into inflamed intestinal tissues (β7-integrin and CXCR3), skin dermis (CCR2 and CCR4), and genitourinary mucous membranes (β1-integrin).

4.1 CXCR3-Expressing Th17 Cell Subsets in Infections

Peripheral blood CM and EM Th17.1 cell levels in acute COVID-19 are lowered compared to control groups [131,202]. It is also associated with an increased CXCR3 ligand, IP-10 [131]. These data suggest that during acute COVID-19, Th17.1 cells migrate to the site of inflammation. After recovery, peripheral blood Th17.1 cell levels returned to the control ranges [132]. The depletion of Th17.1 may be due to both the SARS-CoV-2-triggered hyperactivated immune response and impaired T-helper cell polarization in the secondary lymphoid organs occurring during acute infection. It is plausible that Th17 cells migrate to the site of inflammation with varying efficacy at different stages of the infectious process. Therefore, the data assessing BALF samples are crucial because they indicate Th17 cell accumulation with a pro-inflammatory phenotype in the affected lung tissues [203]. In particular, such Th17 cells had a tissue-resident memory T cell phenotype by expressing the genes associated with cytolytic properties (SRGN, GZMB, and GNLY) and those for the cytokines IL-21, IL-17F, IL-17A, IFNγ, and GM-CSF. Moreover, lung tissues from COVID-19 patients were enriched in CCR6 and IL17A-co-expressing cells, whereas BALF samples contained high concentrations of IL-6, IL-17A, GM-CSF, and IFNγ. Th17 cells might exit the bloodstream at a major stage of the infectious process and migrate into the inflamed lung tissue, where they produce a plethora of proinflammatory cytokines to elicit inflammation and damage to surrounding tissues via diverse mechanisms. Along with this, an important role for Th17 cells in COVID-19 pathogenesis is suggested by the data that, after the successfully reversed infectious process and pathogen elimination, memory Th17 cells remain detected in the circulation. In this regard, some studies reported the development of memory virus-specific Th17 cells producing IL-17A, IL-17F, and IL-22 in response to *in vitro* stimulation with a S-protein-derived peptide pool [136]. Thus, targeting Th17 and theit effector cytokines to manage COVID-19 patients is promising [204].

Previously, it was noted that Th17.1 cells play a hallmark role in the formation of noncaseating granulomas during autoimmune pathologies. In this regard, they were also analyzed for *M. tuberculosis*-caused infections. It is known that this pathology is associated with caseous granulomas formed in various organs. While analyzing peripheral blood Th cell subset composition in TB-infection *in vitro* nonspecific stimulation, it was shown that the level of circulating $CD4^+IL-17A^+$ cells declined, whereas levels of $CD4^+IL-4^+$ T cells significantly increased [205]. For instance, Wang *et al.* [206] found in active TB patients *vs.* control subjects a higher $IL-17^+CD4^+$ T cell level in the circulation that corroborated earlier data showing an increased IL-17 mRNA level in peripheral blood lymphocytes [207]. On the other hand, two independent research groups revealed a decline in peripheral blood Th17 cell levels in TB patients [208,209]. We also found that the circulating Th17.1 cell level was decreased, whereas that of "classical" and $CCR6^+DP$ Th17 cells was significantly increased in patients compared to the control group [210].

To better understand the role of Th17.1 cells in pulmonary tuberculosis, Mtb-specific $CD4^+$ T cell responses were assessed in numerous studies of latent tuberculosis infection (LTBI) and active pulmonary tuberculosis. The study by Nikitina *et al.* [140] showed that $IFN\gamma^+$ lymphocytes represent the major subset of *M. tuberculosis*-specific peripheral blood $CD4^+$ T cells; however, the majority of such cells had the $CXCR3^+CCR6^+$ phenotype. In LTBI, peripheral blood Mtb-specific $CD4^+$ T cells were dominated by the $CCR6^+CXCR3^+CCR4^-$ phenotype, and its percentage increased in patients compared to the control group [211]. Moreover, $CD4^+CCR6^+CXCR3^+CCR4^-$ T cells were unique in the expression of genes associated with enhanced T cell activation in response to tuberculosis infection, as well as increased cell survival and CTL-like-induced cytotoxicity. It is worth noting that such Mtb-specific $CD4^+CXCR3^+CCR6^+$ T cells were almost entirely of the CD45RA-memory Th cell subset in LTBI [212]. In contrast to LTBI, patients with active tuberculosis had Mtb-specific $CD4^+$ T cells less efficiently inducing surface CXCR3 and CCR6 co-expression [213]. Mpande *et al.* [214] demonstrated the development of Mtb-specific stem-like memory T cells (TSCM) in response to primary *M. tuberculosis* infection. Compared to non-specific TSCM, a large quantity of *M.tuberculosis*-tetramer+$CD4^+$ T cells co-expressed CXCR3 with CCR5 and CCR6, along with high expression of granzyme A, granzyme K, and granulysin [214]. Thus, it seems that during tuberculosis infection, Th17.1 cells acquire an effector memory phenotype as well as the potential to migrate to the site of inflammation and secrete granzymes and granulysin, thereby contributing to pathogen elimination and/or limiting the spread of infection.

In HIV infection, $CCR6^+CCR4^+$ Th17 and $CCR6^+CXCR3^+$ Th17.1 cells exert pathogenic effects because they carry *in vivo* integrated HIV DNA, and their levels are significantly lowered in HIV-infected individuals, including those with undetectable plasma viral load during antiretroviral therapy [215]. Similar data were obtained by El Hed *et al.* [216], showing a decreased total Th17 cell count during HIV infection. Moreover, depletion of Th17 and Th17.1 cells in the GALT may be a major cause of microbial translocation, chronic immune activation, and the emergence of non-AIDS-related comorbidities in HIV-infected individuals [217]. Moreover, altered Th17 cell composition in HIV infection is suggested by the data that $CCR6^+DN$ is the most predominant Th17 cell subset in the peripheral blood and lymph nodes of ART-treated HIV-infected individuals, and it is these cells that carry integrated HIV viral DNA [201].

Patients with HCV infection are characterized by a lowered Th17 cell level in the circulation [218], although these data remain controversial [219]. Of note, binding to human sinusoidal endothelium was dependent on $\beta1$ and $\beta2$ integrins, CXCR3, and, in the case of Th17 cells, VAP-1 [220]. Th17 cell recruitment through sinusoids in mice with liver inflammation was downmodulated by using antibodies against CXCR3 ligands, supporting a role for CXCR3 in Th17 recruitment *in vivo*. In the human liver, $IL-17^+$ cells were found in portal infiltrates near CCR6- and CCL20-expressing inflamed bile ducts. Cytokine-treated human cholangiocytes secreted CCL20 and induced CCR6-dependent Th17 cell migration, suggesting that local cholangiocyte-secreted chemokines position Th17 cells in the bile ducts. In addition, HCV-infected patients were shown to have a correlation between Th17 cells and plasma creatinine levels [221]. It should also be noted that virtually no data on the role of $CXCR3^+$ Th17 cells is currently available.

4.2 CXCR3-Expressing Th17 Cell Subsets in Autoimmunity

It should be noted that Th17.1 cells play a critical role in the pathogenesis of multiple sclerosis associated with significantly increased peripheral blood levels, with such cells co-producing IL-17 and $IFN\gamma$. Moreover, Th17.1 cells efficiently transmigrate *in vitro* through the endothelium found in the blood-brain barrier [222]. For example, blood-derived lymphocytes from patients with relapsing multiple sclerosis are strongly prone to differentiation into $IFN\gamma$-producing Th17 cells [223] and are able to migrate across the BBB [224,225], as was confirmed in cerebral autopsy samples [223]. Moreover, a higher level of effector memory Th17.1 cells producing $IFN\gamma$ and GM-CSF was found in the CSF of patients with clinically isolated syndrome and RRMS. A lower percentage frequency of peripheral blood Th17.1 cells is associated with the rapid onset of multiple sclerosis [224]. Hence, checking peripheral blood Th17.1 cell levels in multiple sclerosis may be useful for assessing therapeutic effectiveness. In this regard, a positive effect of

using Natalizumab is linked to an increased level of peripheral blood Th17.1 cells and a long-term absence of relapses [224].

Interestingly, the level of peripheral blood Th17.1 cells is decreased in subjects with rheumatoid arthritis [226]. In addition, synovial fluid in RA *vs.* osteoarthritis patients had a low level of such cells but an increased concentration of CXCR3 ligands (CXCL9 and CXCL10) that was associated with a high infiltration of CXCR3-expressing cells found in immunohistochemistry examination [72]. Thus, it is plausible that during RA, Th17.1 cells migrate to the site of inflammation from the circulation and participate in the formation of tertiary lymphoid structures in joints. As noted by some studies, Th17 cells in RA are able to acquire the Th17.1 phenotype at the site of inflammation due to the high level of pro-inflammatory cytokines, such as IL-12 [227,228]. To support these data, Jimeno *et al.* [229] showed a pathogenic profile for memory Th17 and Th17.1 cells in RA. Baseline peripheral blood Th17.1 cell level in patients with RA may serve as a predictor for response to Abatacept therapy. It should be emphasized that the surface of Th17.1 cells highly expresses the surface MDR-1 protein P-glycoprotein, which accounts for blocking the response to immunosuppressive therapy [199,230]. The percentage of baseline Th17.1 cells but not other Th cell subsets in Abatacept responders *vs.* non-responders was significantly decreased [230]. Also, Th17.1 levels were closely associated with disease activity. RA activity assessed according to the DAS28 scale is inversely correlated with peripheral blood Th17.1 cell level [230]. It is likely that RA Th17.1 cells are involved in autoantibody production. Paulissen *et al.* [231] showed that patients with CCP Ab-positive *vs.* CCP Ab-negative RA had higher surface expression of Th cell CCR6 and CXCR3. Thus, Th17.1 cells in rheumatoid arthritis can be a predictor of response to immunosuppressive therapy and also affect disease course [232].

Indirectly, Th17.1 cells were also noted to play a role in T1D. Marwaha *et al.* [233] demonstrated that Ustekinumab (an anti-IL-17A antibody) in T1D reduced C-peptide and peripheral blood Th17.1 cell levels, which, along with the Th1 subset, may be involved in the lysis of pancreatic beta cells.

On the other hand, Th17.1 cells are also found to exert pathological effects in DCTDs. Thus, patients with SLE were observed to have an increased peripheral blood Th17.1 cell level that was inversely correlated with serum complement component C4 concentration [234]. Th17.1 cells may be involved in the pathogenesis of anti-DNA antibody formation. Zhong *et al.* [235] reported that anti-DNA+ patients with SLE have a higher percentage of CCR6 and CXCR3$^-$ expressing Th cells, including the Th17.1 subset. A rise in peripheral blood Th17.1 cell percentage was also observed in Sjögren's disease [236]. Presumably, this Th cell subset migrates to the site of autoimmune inflammation. Salivary gland IHC from patients with Sjögren's syndrome demonstrates higher infiltration of IFNγ^+IL-17A$^+$ cells [237]. Moreover, peripheral blood Th17.1 cell levels also tend to elevate in patients with autoimmune myositis [238].

In systemic vasculitis, a role for Th17.1 cells was not thoroughly investigated; however, many studies report that its level changed. For instance, Takayasu's arteritis is associated with a higher peripheral blood Th17.1 cell count [239]. Singh *et al.* [239] also observed that they decreased after immunosuppressive therapy based on tacrolimus or metatrexate together with corticosteroids. Furthermore, Th17.1 cell level is also altered in ANCA-positive vasculitis, e.g., in Wegener's granulomatosis, characterized by its decline in peripheral blood EM Th17.1 cell subset [176]. In addition, Liao *et al.* [177] showed an inverse relation between peripheral blood Th17.1 cell level and CRP concentration, as well as a higher risk of poor renal outcomes in ANCA-positive vasculitis.

The percentage of both IL-17- and IL-22-positive Th cells found in patients with AS was higher than in the healthy control group but did not significantly affect the level of IFNγ- and IL-10-positive cells [240]. AS patient-derived cell cultures stimulated *in vitro* contained a supernatant IL-17 level that exceeded that obtained from volunteer samples. All IL-17$^+$ Th cells exhibited CD4$^+$CD45RO$^+$ memory cell phenotype; moreover, the majority of Th cells expressed surface CCR6 and CCR4, and as few as about 50% carried another Th17 cell marker, the IL-23 receptor (IL-23R) . In addition, a significant proportion of IL-17-producing Th cells also synthesized IL-22 and IFNγ, therefore allowing them to be referred to as "classical" Th17 and Th17.1 cells. In addition, it was shown that patients with AS were characterized by increased CCR6$^+$ cell levels in parallel with a reduced count of CXCR3$^+$ lymphocytes among activated (CD25$^+$) peripheral blood Th cells [241]. Moreover, CXCR3 expression was also decreased on memory CD4$^+$ T cells from patients with AS if compared to control subjects.

Currently, only a few studies have analyzed the Th17 cell subset composition in patients with various IBD forms. For instance, it was shown that in IBD, circulating Th cells capable of specifically recognizing antigens derived from intestinal microbiota-derived bacterial cells usually secrete IL-17A, IFNγ, IL-22, and TNFα, allowing them to be referred to as Th17.1 cells [242]. Another autoimmune granulomatous disease, Crohn's disease, is associated with increased infiltration of MDR1-expressing Th17.1 cells into intestinal wall granulomas [199]. This phenomenon may underlie resistance to corticosteroid therapy in IBD patients. Moreover, it is these cells that are involved in maintaining an inflammatory response that results in impaired functioning of adjacent tissues, owing to which they are considered a pathogenic and proinflammatory Th17 cell subset [243]. Patients with Crohn's disease had an in-

creased level of peripheral blood CD45RO$^+$CD4$^+$ T cells able to respond to stimulation by producing cytokines such as IL-17A, IL-21, and IL-22 if compared to the control group [244]. Another study showed that both the percentage and absolute count of peripheral blood IL-17A-producing cells increased in Crohn's disease and ulcerative colitis [245]. Upon this, regulatory T cell levels decreased, which was accompanied by a total decline in the Treg/Th17 ratio in both patient cohorts compared to the control group. Available publications provide evidence that in Crohn's disease, the accumulation of peripheral blood Th17 cells is associated with disease duration [246]. Moreover, the level of IL-17-secreting Th cells in peripheral blood was closely related to the severity of Crohn's disease [247].

In sarcoidosis, Th17.1 cells are involved in the formation and maintenance of granulomatous inflammation in the affected organs. Also, they can serve as a prognostic factor, mirroring disease chronicity. A rise in peripheral blood and BALF Th17 cell levels in patients with Löfgren's syndrome was a predictor for the resolution of the acute process without sarcoidosis chronicity [248]. Furthermore, Lazareva et al. [249] noted that the frequency of peripheral blood DP Th17 was significantly increased in patients with chronic and Löfgren's syndrome vs. the control group, while "non-classical" Th17.1 was shown to have a significantly reduced level only in chronic sarcoidosis vs. healthy subjects. However, Th17 cells migrating to the site of inflammation can transform into the Th17.1 phenotype, which promotes granuloma formation and sustained chronic inflammation. For instance, BALF Th17.1 cell level was higher in patients with chronic disease than in patients with disease resolved within a 2-year clinical follow-up [250]. A immunohistochemistry examination revealed a higher Th17.1 level both in the sarcoid granuloma center and periphery [251,252], reflecting their possible role in autoimmune inflammation. Examining peripheral blood in patients with chronic pulmonary sarcoidosis reveals both a rise [252] and a decline [253] in CD4$^+$CCR6$^+$CXCR3$^+$ T cell levels. Despite this, Th17.1 cells in patients with chronic pulmonary sarcoidosis migrate to the site of inflammation, which agrees with recent studies. Moreover, Ramstein J et al. [254] showed that a higher Th17.1 cell level is found in mediastinal lymph nodes and BALF vs. peripheral blood in chronic pulmonary sarcoidosis. Thus, Th17.1 cells in chronic sarcoidosis migrate to the site of inflammation, promote granuloma formation via macrophage chemotaxis and activation [251], and serve as a negative predictor of disease course. At the same time, some studies report a favorable disease prognosis and granuloma resolution upon increased T-bet$^+$RORgT$^+$CD4$^+$ T cell levels in the BALF of patients with Löfgren's syndrome [255]. However, T-bet$^+$RORgT$^+$CD4$^+$ T cells may represent transitional Th17.0 cells acting as Th17.1 precursors yet lacking CXCR3 expression [256].

It should be noted that the Th17.1 subset plays an important role in the pathogenesis of psoriasis because it promotes keratinocyte apoptosis and proliferation in skin lesions [257]. Also, Th17.1 correlates with disease severity [258]. Tsiogkas et al. [259] showed an increased content of CD3$^+$CD4$^+$CXCR3$^+$ T cells and CXCR3 expression among the CD3$^+$CD4$^+$CCR6$^+$CCR4$^-$ and CD3$^+$CD4$^+$CCR6$^+$CCR4$^+$ lymphocytes in the peripheral blood of patients with psoriasis. The elevated levels of these cells in the circulation may be due to high antigenic stimulation occurring in peripheral lymphoid organs. Next, they migrate into the dermis, as evidenced by Lowes et al. [260]. Moreover, Tsiogkas et al. [259] showed that anti-IL-17A monoclonal antibodies downmodulate Th17 (CD3$^+$CD4$^+$CCR6$^+$), Th1 (CD3$^+$CD4$^+$CXCR3$^+$), and Th17.1 (CD3$^+$CD4$^+$CCR6$^+$CCR4$^-$CXCR3$^+$) cell frequencies as well as CXCR3 expression on CD4$^+$CCR6$^+$CCR4$^+$ and CD4$^+$CCR6$^+$CCR4$^+$ cell types in patients with psoriasis 3 months post-treatment. Thus, similar to systemic autoimmune pathologies, Th17.1 cells are also directly involved in autoimmune skin disorders.

In infections, the role of Th17.1 requires further investigation. However, the data, although controversial, hints at the protective role of these cells. Th17.1 also forms a memory phenotype and acquires cytolytic activity against intracellular pathogens. This feature might reflect their positive impact on infectious diseases, although it is followed by the attraction of neutrophils and the death of the host's cells. In autoimmunity, we see the same controversy concerning Th17.1 dynamics. It happens due to the technical disparities when analyzing these cells, a lack of standardization in methodology, and a shortage of accessible data on the topic.

In autoimmune diseases, Th17.1 cells exhibit a wide range of pathogenic functions and are able to migrate to sequestered organs, initiate and maintain autoimmune inflammation, and contribute to disease progression. Moreover, the Th17.1 cell phenotype often underlies resistance to immunosuppressive therapy in autoimmune pathologies.

5. CXCR3-Expressing Follicular Th Cell Subsets in Infections and Autoimmunity

T follicular helper (Tfh) cells play an essential role in B cell maturation and differentiation during the germinal center reaction in peripheral lymphoid organs [261,262]. These cells control antibody class switching, triggering somatic hypermutations, and selecting high-affinity B cell clones, which subsequently differentiate into plasma cells and memory cells. At present, Tfh cells circulating in the peripheral blood are considered a heterogeneous population that may be subdivided into several independent lineages based on the co-expressed chemokine receptors CCR6 and CXCR3, as well as the presence of various transcription factors typical of polarized Th cell subsets [263]. For instance, Th1-like Tfh or Tfh1 cells bear solely surface CXCR3 along

with the transcription factor T-bet, whereas Th2-like Tfh or Tfh2 cells lack both of the above-noted chemokine receptors but express transcription factor GATA3 at a high level. And finally, Th17-like Tfh or Tfh17 cells display the CXCR3$^-$CCR6$^+$RORγt$^+$ phenotype [263]. Moreover, apart from the phenotype and expression of transcription factors characteristic of polarized Th cells, Tfh cells may produce and secrete key cytokines so that, in response to *in vitro* stimulation, Tfh1, Tfh2, and Tfh17 cells produced IFNγ, IL-4, IL-13, and IL-17, respectively. In addition, such Tfh cell subsets differ in functional activity regarding B cells, at least in an *in vitro* co-culture setting. It was shown that Tfh17 and Tfh2 cells stimulated 'naïve' B differentiation into plasma cells, which was accompanied by antibody class switching and increased immunoglobulin levels released. In contrast, Tfh1 cells induced apoptosis and prevented 'naïve' to-effector B cell transformation. Relatively recently, a CXCR3$^+$CCR6$^+$ Tfh cell subset called Tfh17.1 cells was described in the peripheral blood of patients with common variable immunodeficiency, although their functional activity has not been detailed [264].

5.1 CXCR3-Expressing Follicular Th Cell Subsets in Infections

Using experimental animal models allowed us to show that IFNγ-secreting Th17 cells negatively affect the formation of long-term immune protection against repeated *M. tuberculosis* infection, whereas accumulation of lung CXCR5$^+$ Th17 cells enhances the effectiveness of protective reactions, at least in mice [265]. Granuloma immunohistology analysis of specimens obtained in an experimental mouse *in vivo* model [266] as well as primate *M. tuberculosis* infection [267] and Mtb patients [268] revealed clusters consisting not only of CD3$^+$ but also CD19$^+$ lymphocytes in lymph node germinal center-like structures containing proliferating B cells. Moreover, the formation of highly organized ectopic lymphoid structures containing CXCR5$^+$ T cells in granuloma was closely related to favorable outcomes in latent TB infection, whereas poorly organized or diffuse lymphoid structures with low Tfh cell levels were observed in active TB and exerted weak protective properties against *M. tuberculosis* [269]. Finally, another study also showed that CD4$^+$CXCR5$^+$ lymphocytes might produce IFNγ, allowing us to refer them to the Tfh1 cell subset. During *M. tuberculosis* infection, we observed an altered Tfh cell subset composition associated with a higher level of circulating CXCR3$^-$CCR6$^-$ Tfh2 cells along with a lowered percentage of CXCR3$^+$CCR6$^-$ Tfh1 cells, whereas no significant changes in the percentage of the remaining Tfh17 and DP Tfh cells were noted [210]. Disturbed functional activity of circulating Tfh cells was observed in the study by Kumar *et al*. [270] in active TB infection. It was shown that not only the percentage of peripheral blood IL-21-producing cells but also the serum IL-21 level were reduced. Moreover, the IFNγ level commonly associated

with the Tfh1 cell subset was also decreased in patients with TB, thereby corroborating our data describing altered Tfh cell subset composition in the latter.

Patients during acute COVID-19 were found to have an imbalanced ratio between peripheral blood CXCR3$^+$CCR6$^-$Tfh1 cells due to a decreased percentage of regulatory Tfh1 and an increased level of pro-inflammatory Tfh17 cells [202]. COVID-19 convalescent patients had circulating virus S-protein-specific CD45RA$^-$CXCR5$^+$ Tfh cells along with an extremely low percentage of RBD-specific Tfh cells [271]. Moreover, the vast majority of SARS-CoV-2-specific Tfh cells belonged to the CCR6$^+$CXCR3$^-$ Tfh17 subset, and only a few of them had the Tfh1 phenotype (CCR6$^-$CXCR3$^+$). A high count of cTfh1 and cTfh2 cells was positively correlated with high serum neutralizing activity in COVID-19 convalescent patients [271]. At the same time, after acute COVID-19, a change in peripheral blood Tfh cell subset composition was observed, which could persist long-term. Interestingly, COVID-19 convalescents might have elevated Tfh levels within several months after recovery, which was closely related to a higher percentage of Tfh2 and Tfh17 cells [272]. Similar data was obtained by Similar results were obtained by Gong *et al*. [135], who noted an increase in the proportion of CXCR3$^+$CCR6$^+$ Tfh1 and CXCR3$^+$CCR6$^+$ Tfh2 cells compared to the control, while the level of CXCR3$^+$CCR6$^+$ Tfh17 was significantly reduced. The high activity of Tfh1 cells in COVID-19 convalescents may contribute to the initiation of chronic autoimmune inflammation [273].

Recently published data revealed that lymph node germinal center (GC-Tfh) Tfh cells are reservoirs for HIV and simian immunodeficiency virus (SIV). The number of GC-Tfh cells increases during chronic HIV and SIV infection [274–276], which is considered a highly favorable prognostic parameter of the HIV and SIV infection course [277, 278]. In addition, it was shown that productive SIV infection occurs in resident intrafollicular CD4$^+$ Tfh cells in the lymph node B-cell follicles of SIV-infected elite controller rhesus macaques [279] and is protected from cytotoxic CD8$^+$ T cells. It was hypothesized that latent infection is established in circulating memory CD4$^+$ T cells when they pass through a chemokine-rich environment such as lymph nodes [149,280]. Using activation-induced marker assays, Niessl *et al*. [281] assessed CXCR3 and CCR6 expression on activation-induced Ag-specific cTfh cells in Antiretroviral therapy (ART)-treated individuals. HIV$^-$ and CMV$^-$ specific cTfh cells were dominated by Th1-like (CXCR3$^+$CCR6$^-$) phenotype cells, whereas HBV-specific cTfh cells showed a mixed cTfh profile with Th2-like (CXCR3$^-$CCR6$^-$) and Th1-like polarization. However, a large percentage of Ag-specific CXCR3$^+$ cTfh cells also produce the Tfh cell cytokines CXCL13 and IL-21. Altogether, a co-expression assay revealed a higher CXCL13

and IL-21 level, along with Tfh cell cytokines and IFNγ co-expressed by HIV-specific *vs.* CMV-specific cTfh cells [281].

It was shown that HCV infection is accompanied by cTfh cells skewed towards differentiation of CXCR3$^+$ cTfh cells highly expressing Tfh-associated molecules, including Programmed cell death 1 (PD-1), Inducible T-cell costimulator (ICOS), IL-21, and Bcl-6, compared to CXCR3$^-$ cTfh cells [282]. Along with this, the level of circulating CXCR3$^+$ cTfh cells positively correlated with HCV titers and nAbs. Moreover, cTfh cells and autologous memory B cells co-cultured *in vitro* showed that CXCR3$^+$ *vs.* CXCR3$^-$ cTfh cells promoted clonal expansion of HCV E2-specific B cells from HCV-infected individuals. Such data suggest that HCV infection promotes cTfh cell expansion and skews cTfh cells toward CXCR3$^+$ cTfh cell differentiation, which aligns with the study showing that the majority of MHC II tetramer-positive antigen-specific CD4$^+$ T cells express CXCR3 and exhibit properties similar to Tfh cells during acute infection with HCV [283]. It should be noted that the presence of activated ICOS$^+$CXCR3$^+$ Tfh cells is closely related to effective antibody production and the successful resolution of HCV infection [284]. Also, in chronic HCV infection, the level of peripheral blood Tfh1 (IFNγ^+CD4$^+$CXCR5$^+$) and Tfh2 (IL-4$^+$CD4$^+$CXCR5$^+$), but not Tfh17 (IL-17$^+$CD4$^+$CXCR5$^+$) cells was noted to rise compared to the control group [285].

5.2 CXCR3-Expressing Th Follicular Cell Subsets in Autoimmunity

Patients with relapsing and secondary progressive multiple sclerosis were characterized by a lowered percentage of Th1-like Tfh cells, whereas in PPMS it was increased [286]. Another study showed that the Tfh subset cell composition in RRMS undergoes profound change related to a decreased percentage of Tfh2 cells and an increase in the proportion of Tfh17.1 cells among total CD45RA$^-$CXCR5$^+$ Th cells [287]. It should also be emphasized that the percentages of Tfh1 and Tfh17 cells in MS patients and the comparison group did not significantly differ, which may suggest a pro-inflammatory shift in Tfh cell polarization. The use of the first-line drug dimethyl furamate was accompanied by gradually increased Tfh2 along with decreased Tfh1 and pathogenic Tfh17.1 cells in the total Tfh cell population. It should also be noted that dimethyl furamate was able to reduce both serum IgA, IgG2, and IgG3 levels as well as memory IgD$^-$CD27$^+$ B cell levels, which underwent antibody class switching. Choileáin *et al.* [288] noted in relapsing-remitting multiple sclerosis (RRMS) a higher percentage of cTfh1 (CXCR5$^+$CXCR3$^+$CCR6$^-$) cells, but that of cTfh1-Tfh17 (CXCR5$^+$CXCR3$^+$CCR6$^+$) and cTfh17 (CXCR5$^+$CXCR3$^-$CCR6$^+$) cells remained unaltered. Moreover, Haque *et al.* [289] showed that the percentage of CXCR3$^-$CCR6$^+$ Tfh17 and CXCR3$^+$CCR6$^+$ Tfh17.1 within CXCR5$^+$PD1$^+$ Th cells in multiple sclerosis (MS) patients increased compared to control subjects. On the other hand, Tfh17.1 cells were dominated by *in vitro* IL-21 production, so the level of IL-21$^+$ Tfh17.1 cells in MS patients exceeded that in the control group. Finally, CSF from patients with MS was characterized by increased levels of CXCR3$^+$CCR6$^+$ cTfh1 and CXCR3$^+$CCR6$^+$ cTfh17.1 cells [290]. Thus, these data suggest that Tfh17.1 cells may represent one of the crucial arms in MS pathogenesis, although more detailed studies regarding their role in the formation of autoreactive B cell clones and foci of tertiary lymphoid tissue in MS are required.

While analyzing Th cell subset composition from patients with rheumatoid arthritis, it was shown that patients with high (DAS28 $\geq$5.0) *vs.* low (3.2 < DAS28 < 5.0) disease activity had increased Tfh2 and Tfh17 cell levels, whereas that of CXCR3$^+$CCR6$^-$ Tfh cells differed insignificantly both between the compared groups and control subjects [291]. A rise in Tfh2 cell level was also noted by Takeshita *et al.* [292] in patients with first-diagnosed untreated RA compared to control subjects. Moreover, higher peripheral blood Tfh17 cell levels were closely related to increased anti-citrullinated protein antibodies (ACPAs) titers [293]. Interestingly, therapeutic TNFα blockade had no effect on Tfh17 cell levels, which remained consistently high in RA patients *vs.* the control group [294]. At the same time, another study was unable to observe significantly differing levels of CXCR3$^+$CCR6$^-$ (Tfh1), CXCR3$^-$CCR6$^-$ (Tfh2), and CXCR3$^-$ CCR6$^+$ (Tfh17) cells in rheumatoid arthritis, undifferentiated arthritis, and control subjects [295]. Moreover, Arroyo-Villa *et al.* [296] noted that in patients with RA, there was a higher percentage of pro-inflammatory Tfh cell subsets calculated by the formula (%Tfh-Th2 + %Tfh-Th17)/%Tfh-Th1 in RA patients *vs.* the control group, whereas the level of some Tfh cell subsets was within the normal range.

An experimental model of type 1 diabetes mellitus revealed that pancreatic CXCR3$^+$CCR6$^-$Tfh1 but not CXCR3$^-$CCR6$^+$ Tfh2 and CXCR3$^+$CCR6$^+$ Tfh17 cell levels were higher in SAP–/–/NOD *vs.* Wild type/Non-obese diabetic (WT/NOD) mice [297]. On the other hand, no significant change in CXCR5$^+$ T cells expressing different CXCR3 and/or CCR6 patterns was observed in T1D patients *vs.* the control group [298].

On the contrary, patients with active SLE (SLEDAI score >8) were characterized by a slightly different Tfh cell subset distribution, primarily having significantly increased Tfh2 cell levels paralleled with a decline in Tfh1 cells [299]. However, alterations in Tfh2 and Tfh1 cell frequencies were closely related to high serum immunoglobulin and autoantibody levels. Moreover, a decreased percentage of peripheral blood Tfh1 cell level was inversely associated with the SLEDAI score, whereas that for Tfh2 cells became elevated while the SLEDAI score increased. Along with

that, patients with active *vs.* inactive SLE had a markedly higher Tfh2 cell level. Serum anti-dsDNA autoantibodies were associated with elevated Tfh2 and decreased Tfh1 cells compared with patients who lacked anti-dsDNA antibodies. Moreover, serum IgE concentration in SLE correlated with a high percentage of Tfh2 subset cells, which indirectly provides evidence about a role for Tfh2 cells in triggering IgE secretion, previously described by Morita *et al.* [263]. At the same time, an increased percentage of peripheral blood $CXCR3^+CCR6^-PD\text{-}1^+CXCR5^-CD4^+$ Tfh cells was found in SLE [171]. In addition, it was also found out that $CXCR3^-CCR6^+$ Tfh17 cell levels solely decreased in SLE, whereas Tfh1, Tfh1/17, and Tfh2 subset cells were within the normal range [300]. The data obtained by Mao *et al.* [301] uncovered a higher percentage of the $CXCR5^+CD45RA^-CD4^+$ Tfh17 subset in the total Tfh cell subset. Moreover, patients with active SLE had a lower peripheral blood $CXCR3^+CCR6^-$ Tfh1 cell level, whereas that of Tfh2 cells correlated with the level of circulating plasma blasts and anti-dsDNA autoantibodies. A decline in $CXCR3^+CCR6^-$ Tfh1 cells could be related to their potential to migrate to the sites of inflammation, as evidenced by histology studies and the observed inverse relation between the level of such cells and the SLEDAI score [302]. On the other hand, it was also shown that the levels of key Tfh1 cell subsets—Tfh1, Tfh2, and Tfh17—did not differ significantly between patients with active SLE, inactive SLE, and control subjects, but PD-1 expression on all Tfh cell subsets analyzed in active SLE was superior to the remaining two groups [303].

In Sjögren's syndrome, the level of peripheral blood $CD4^+CXCR5^+$ T cells becomes elevated compared to the control group [304]. This was primarily due to the higher percentage of circulating Tfh cells displaying the $CXCR5^+CCR6^+$ phenotype, considered a distinct cell population called Tfh17. Moreover, a direct correlation between increased Tfh17 levels and clinical signs such as the level of immunoglobulins, anti-Ro/anti–Sjögren's-syndrome-related antigen A autoantibodies (SSA), anti-La/anti–Sjögren's-syndrome-related antigen B autoantibodies (SSB), and EULAR Sjögren's syndrome (SS) disease activity index (ESSDAI) scores was found. The percentage of $CXCR3^-CCR6^-$ (Tfh2) and $CXCR3^-CCR6^+$ (Tfh17) tended to rise in parallel with the decreasing level of $CXCR3^+CCR6^-$(Tfh1) Tfh cells noted by Kim *et al.* [305], although no significant differences were identified as compared with the control group. Another study revealed no significant differences while analyzing the levels of $CXCR3^+CCR6^-$ Tfh1, $CXCR3^+CCR6^+$ Tfh1/17, $CXCR3^-CCR6^-$ Tfh2, and $CXCR3^-CCR6^+$ Tfh17 cells in Sjögren's syndrome *vs.* control subjects [306]. Similar data were also obtained in an experimental mouse model of Sjögren's disease (NOD/ShiLtJ mice), demonstrating an increased level of Tfh cells ($CD4^+CXCR5^+PD1^+$), whereas for individual splenic subpopulations such as Tfh1,

Tfh2, and Tfh17, their level did not change significantly compared to the control group [307]. At the same time, $CD4^+CXCR5^+$ Tfh cell clusters were found in affected salivary glands [308], whereas upregulated expression of Tfh-associated molecules (Bcl-6, IL-21, and CXCR5) was closely associated with disease progression [309].

Before the onset of therapy, patients with ankylosing spondylitis had a higher level of $CD4^+CXCR5^+CXCR3^+CCR6^+$ Tfh1 cells, whereas the percentage of $CD4^+CXCR5^+CXCR3^+CCR6^+$ Tfh17 lymphocytes was decreased compared to the control group; no inter-group differences were found in Tfh2 cell level [310]. On the other hand, Yang *et al.* [311] revealed in patients with AS a decline in the percentage of $CXCR3^+CCR4^+CXCR5^+$ Tfh1 cells along with an elevated level of $CXCR3^+CCR4^+CXCR5^+CCR6^+$ Tfh17. Our personal studies uncovered that the central memory $CXCR5^+CD45RA^-CD62L^+$ Th population contained a lower level of Tfh1 cells in parallel with a higher percentage of Tfh2 and Tfh17 cells, and an imbalance between these cell types was associated both with Ankylosing Spondylitis (AS) exacerbation and remission [312].

Similar changes manifested as a decreased level of peripheral blood $CXCR3^-CCR6^+$ Tfh17 cells and a rise in the percentage of $CXCR3^-CCR6^-$ Tfh2 cells were described in ulcerative colitis [313]. Regarding Crohn's disease, a single relevant work is currently available showing that peripheral blood Tfh1- and Tfh17-like cell levels displaying the phenotypes $CXCR3^+CCR6^-$ and $CXCR3^+CCR6^+$ (although recently, such cells are commonly called Tfh17.1-like lymphocytes) were increased relative to the control group, whereas that of Tfh2-like cells ($CXCR3^-CCR6^-$) did not differ significantly from control subjects [314]. Hence, in some autoimmune diseases, not only changes in Tfh subset composition may be observed, but they may be related to the clinical picture and severity of pathological processes.

Patients with IgG4-related disease contained a higher percentage of Tfh2 cells compared to control subjects and patients with primary Sjögren's syndrome [315,316]. Moreover, a high positive relation was also revealed between circulating Tfh2 cell level and IgG4 concentration as well as IgG4:IgG ratio, and a relationship between Tfh2 cell percentage and level of peripheral blood circulating $CD19^+CD20^-CD27^+CD38^+$ plasma cell precursors as well as IL-4 level were also shown. Similar data were obtained by Grados *et al.* [317], who noticed that the rise in circulating $CD4^+CXCR5^+PD1^+$ Tfh cells was primarily associated with a higher percentage of Tfh2 as well as Tfh17 cells. Another study noted an increased percentage of Tfh1 and Tfh17 cells in patients with active disease compared to control subjects, so that the level of Tfh1 cells was positively correlated not only with IgG4 concentration but also with disease activity according to the IgG4-related disease (RD) responder index (RI) scale scores [318].

Patients with sarcoidosis examined by us revealed an increased level of circulating CXCR3$^-$CCR6$^-$ Tfh2 cells, whereas the percentage of CXCR3$^+$CCR6$^-$CCR4$^-$ Tfh1 and CXCR3$^+$CCR6$^+$CCR4$^-$ Tfh17.1 cells was significantly reduced relative to the control range [319]. Moreover, an altered Tfh1/Tfh2/Tfh17 cell balance was noted not only in peripheral blood but also in the BALF samples from patients with sarcoidosis [320,321]. A marked role for diverse Tfh cell subsets was also indicated by identifying them in lung lesions [322].

The prevalence of peripheral blood Tfh17 cells in psoriasis patients was significantly increased along with Tfh2 and Tfh1 cell percentages that tended to increase and decrease, respectively [323,324]. Moreover, the level of Tfh17 cells positively correlated with the volume of skin layer lesions, psoriasis area, and severity index (PASI). In response to therapy that alleviates psoriasis symptoms, the percentage of circulating Tfh17 cells also decreased. Similar data were obtained by Liu *et al*. [325], who showed a higher percentage of circulating Tfh17 cells with the PD-1$^+$CXCR5$^+$ phenotype that also correlated with disease severity and serum CXCL13 level. These data indicate a crucial role of Tfh cells as well as the CXCL13/CXCR5 axis in psoriasis pathogenesis and can also be considered a promising therapeutic target. Patients with Graves' disease were found to have a significantly increased level of Tfh2 cells (CXCR3$^-$CCR6$^-$) compared to the control group, whereas for Tfh1 (CXCR3$^+$CCR6$^-$) and Tfh17 (CXCR3$^-$CCR6$^+$) cells, it was decreased in total CD4$^+$ T cells [326]. Patients with myasthenia gravis were found to have circulating Tfh2 and Tfh17 cells at significantly higher levels than in the control group, whereas the percentage of Tfh1 cells that remained intact did not differ from the control [327]. A rise in peripheral blood Tfh17 but not in Tfh1 and Tfh2 cells was also observed in patients with MuSK-antibody-positive myasthenia gravis [328]. Yang *et al*. [329] also reported that patients with myasthenia gravis have high levels of peripheral blood Tfh17 *vs.* other Tfh cell subsets, which also highly express ICOS, PD-1, and IL-21, suggesting their activation. Moreover, the level of cTfh-Th17 cells correlated with that of plasma cell precursors and anti-acetylcholine receptor (anti-AChR) antibodies. A type of Guillain-Barré syndrome called acute motor axon neuropathy was noted to be associated with an increased level of circulating Tfh cells [330]. Such patients had a higher absolute count of the major Tfh subsets, such as Tfh1, Tfh2, and Tfh17, that exceeded not only its magnitude in the control group but also that found in acute inflammatory demyelinating polyradiculoneuropathy. Apart from this, such patients had an increased percentage of Tfh2 and Tfh17 cells compared with the above-noted groups, whereas Tfh1 cell levels did not differ significantly.

Follicular T cells and their subpopulations are quite new; therefore, our understanding of their bilogy and function is limited. At the same time, we can presume that there is a balance between pro-inflammatory CXCR3$^+$ Tfh1 cells and anti-inflammatory Tfh2 and Tfh17 cells. This balance is crucial for the effective functioning of the humoral part of antigen-specific immunity. For effective responses against intracellular pathogens, it is important to have high levels of Tfh1 circulating cells; this allows them to migrate throughout the lymphoid tissues and regulate the functions of antigen-specific B cells in regional lymph nodes and lymphoid nodules in the gut.

In autoimmune diseases, an imbalance between Tfh cells can be associated with autoantibody production. Moreover, in some cases, the imbalance can be related not only to the decrease of Tfh1 in circulation but also to the increase of Tfh2 and/or Tfh17 while Tfh1 levels stay within the norm. Therefore, when analyzing different Tfh populations, it is important to consider the balance between pro- and anti-inflammatory cell types. However, it is the different types of Tfh cells and their cytokines that can be used as targets for biological therapy in autoimmunity.

6. CXCR3-Expressing Regulatory Th Cell Subsets in Infections and Autoimmunity

Regulatory Th cells (Tregs) mainly target innate (tissue macrophages, antigen-presenting cells, and natural killer cells) and adaptive immune (effector cytotoxic T lymphocytes and T helper cells, as well as B lymphocytes) cells. For this, Tregs enable diverse mechanisms traditionally divided into "non-contact" (mediated by various Treg-released soluble molecules, which diffuse in tissue fluids) and "contact" (mediated by interaction between Treg receptors and surface ligands on target cells) effects [331]. The ability to exhibit regulatory properties varies markedly among different Treg subsets, which can be detected by assessing the expression of various surface and intracellular markers. Chemokine receptor CXCR3 and CCR6-based Treg classification allows to divide total memory Tregs into Th1-, Th2-, and Th17-like Treg subsets [332,333]. For instance, Th1-like Tregs are characterized by transcription factor T-bet, surface CXCR3 expression, and IFNγ production, whereas Th2-like Tregs typically contain GATA3 and Th2 cytokines, including IL-4, IL-5, and IL-13, but Th17-like Tregs are described as CCR6$^+$ IL-17A-secreting RORγt-positive lymphocytes [334,335].

In the case of Tregs, CXCR3 expression was observed not only on memory cells but also on around 10% of CD4$^+$CD45RA$^+$CD45RO$^-$CD25^{hi}CD127^{lo} 'naïve' Tregs [332]. CXCR3$^+$ Tregs are commonly recognized as a highly specialized population of Th1-like Tregs that in humans may differentiate *in vitro* after exposure to cytokines such as IL-12, IFNγ, and IL-27, although such cells are also found in the peripheral blood of healthy individuals. It was shown that IL-12 triggers expression of the transcription factors T-BET and CXCR3 via the activated STAT4 pathway, whereas IFNγ and IL-27 elicit it through the STAT1 signaling cascade [336]. Phenotypic

profiling of CXCR3$^+$ Th1-like Tregs and other Treg subsets such as CXCR3$^-$CCR6$^+$CCR4$^+$CCR10$^+$ Th22-like Tregs, CXCR3$^-$CCR6$^+$CCR4$^+$CCR10$^-$ Th17-like Tregs, as well as CCR6$^-$CXCR3$^-$CCR4$^+$ Th2-like Tregs showed that they expressed transcription factors FoxP3, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and Helios at comparable levels [332]. Moreover, all of the above-noted Treg populations showed similar potential to suppress *in vitro* proliferation of autologous CD4$^+$ T cells. However, *in vitro*-stimulated Th1-like Tregs were able to produce a weak level of IL-10 as well as IFNγ. Finally, expression of the transcription factor T-bet (TBX21) typical of diverse Th1-like cells was detected in CXCR3$^+$ Th1-like Tregs co-expressing increased levels of CD73 and TGF-β1 compared to other Treg subsets [337]. T-bet$^+$ Treg cells are also characterized by highly expressed TIGIT, closely related to both high IL-10 production and the potential to skew dendritic cell differentiation towards a tolerogenic phenotype [338,339]. Altogether, it allows us to consider CXCR3$^+$ Th1-like Tregs as one of the most effective suppressors among diverse human Treg subsets. Using *in vivo* experimental models, it was shown that CXCR3$^+$ Tregs were able to migrate along a CXCL10 gradient to the sites of inflammation, where they prominently suppressed effector responses mediated by Th1 cells and relevant target cells [6,340]. Furthermore, *in vitro* IL-12-treated Th1-like Tregs began to produce IFNγ and lost their suppressive potential, which, however, could be reversed by adding anti-IFNγ antibodies or removing IL-12 from cell culture medium [341]. Thus, Th1-like Treg cells may acquire effector functions and secrete inflammatory cytokines like normal Th1 cells in specific settings. Perhaps it may precisely account for multiple observations in various autoimmune diseases describing Treg cells producing pro-inflammatory rather than anti-inflammatory cues at the site of inflammation.

6.1 CXCR3-Expressing Regulatory Th Cell Subsets in Infections

During infections, CXCR3$^+$ Th1-like Tregs may migrate to the site of pathogen entrance and decrease efficacy of innate and adaptive immune responses fighting against microbes. The pathogenic role of for such cells is of special importance in type 1 inflammatory reactions aimed at clearance of pathogens localized inside host cells shown, e.g., in viral infections, including COVID-19.

In COVID-19, increased circulating Treg levels were typical of severe forms of the disease and were also strongly associated with poor outcomes [342]. On the other hand, it was shown that peripheral blood Treg levels progressively increased with COVID-19 severity escalating from mild to severe forms but abruptly decreased in critically ill patients [343]. Moreover, an association between higher CXCR3$^+$ Treg levels and disease severity was also shown [344]. Apart from this, Tregs from patients with severe COVID-19 were characterized by upregulated expression of markers associated with Th1 cells such as CXCR3, GZMK, IL12RB1, and T-bet [342]. In addition, the effect of altered Treg subset composition and functional activity in post-COVID-19 syndrome has been extensively debated [345]. In this regard, the former parameter remained disturbed for up to 6 months even after mild COVID-19 [346], but some studies suggest that both of them may recover to the normal range [347,348].

A higher CXCR3$^+$ Treg level was observed in patients with HIV infection [349]. Similar data were reported by Yero *et al*. [350], also noting that before ART, the percentage of circulating CXCR3$^+$ Tregs increased in HIV-infected patients but progressively decreased during therapy.

A crucial role for Th1-like Tregs was demonstrated in liver lesions during chronic hepatitis C virus infection [351] as well as lethal oral Toxoplasma gondii infection in mice [352]. Surface OX40 expression is found to coincide with IFNγ expression and Treg function in Tregs isolated from liver tissue from patients with hepatocellular carcinoma and HCV cirrhosis [351]. These data suggest that OX40 expression effectively distinguishes Th1-like (OX40$^-$) Tregs with IFNγ expression coupled to reduced suppressive function from Th1-suppressive (OX40$^+$) Tregs. In this study, cirrhotic liver tissue and tumor microenvironment were shown to favor accumulation of OX40$^+$ Th1-suppressive Tregs, whereas OX40$^-$Th1-like Tregs preferentially accumulated in non-cirrhotic HCV-associated liver tissue. OX40$^-$related stimulation may abrogate Treg function, therefore allowing us to assess it as a potential antitumor target [353].

In infectious processes, both resident tissue cells and effector T cells may trigger Tregs expression of transcription factor T-bet and IFNγ production. Apparently, Th1-like Tregs emerging during acute infections may act as a physiological defense mechanism, whereas their increased level in autoimmune diseases can potentially deteriorate the disease course and outcome.

6.2 CXCR3-Expressing Regulatory Th Cell Subsets in Autoimmunity

A whole body of clinical and experimental data revealed that altered Treg cell levels in the bloodstream as well as phenotypic changes and dysfunction at the site of inflammation are related to a high risk of developing human autoimmune diseases [354].

Using *in vivo* experimental models allowed us to show that CXCR3 and its ligands play a crucial role in the migration of CXCR3$^+$ Tregs into nervous tissue, accompanied by a lowered severity of experimental autoimmune encephalomyelitis (EAE) [35,355]. In addition, a rise in CXCL10 as a key ligand for CXCR3$^+$ Tregs was found in nervous tissue lesions, whereas the EAE model in CXCR3$^{(-/-)}$ mice observed reduced CXCR3$^+$ Treg in-

filtration into lesions accompanied by severe chronic inflammation and stronger demyelination and axonal damage [355]. Also, a high level of CXCR3 ligands was found in nervous tissue lesions in patients with MS [156,356]. For instance, MS patients had a higher IFNγ-producing Treg level with a CD4$^+$CD45RA$^-$CD25^{hi}CD127^{low} phenotype compared to the control group [341]. It is believed that Treg PI3K/AKT/Foxo1/3-axis plays an essential role in triggering IFNγ production of Tregs by cells [357]. Moreover, it was this signaling pathway that was activated in patients with RRMS compared to the control group, and its *in vitro* blockade contributed to suppressed IFNγ production and the recovery of Treg suppressive properties. In addition, another study showed a downregulated level of CXCR3$^+$CCR6$^+$ Tregs with the CD4$^+$CD25$^+$CD127lo phenotype compared to the control group [358]. It appears that CXCR3$^+$ Tregs in MS patients may effectively enter inflamed nervous tissue, but their functional properties may be impaired, as shown in a series of *in vitro* experiments (summarized in [359] and [360]).

Patients with rheumatoid arthritis were shown to have significantly lower Th1-like Treg levels in parallel with elevated ESR and CRP levels, as well as a high level of anti-cyclic citrullinated peptides (anti-CCP) and anti-mutated citrullinated vimentin (anti-MCV) autoantibodies, whereas the level of Th1-like Tregs in the joint capsules was negatively correlated with the DAS28 scale [337]. However, Th1-like Tregs from RA patients could not effectively block *in vitro* T-cell proliferation assessed in functional tests, indicating thereby that their suppressive properties were impaired for yet unknown reasons. Similar data were obtained by Kommoju *et al*. [361], showing higher levels of CXCR3$^+$ Tregs in peripheral blood and SF from patients with RA, as well as a direct relation between their level and seropositivity along with disease activity. Children with oligoarticular juvenile idiopathic arthritis, the most common form of chronic inflammatory arthritis, were found to have synovial fluid Tregs dominated by phenotype, with highly expressed CXCR3, IFNγ, T-bet, and CD161 allowing them to be referred to as Th1-like Tregs. Whereas Th17-like Treg levels were significantly decreased [362]. At the same time, it was also evidenced that RA patients are characterized by an increased level of Th17-like Tregs capable of producing IL-17 and exerting lower anti-inflammatory properties [363]. Moreover, collagen-induced arthritis in the RA mouse model was also associated with downmodulated Foxp3 expression upon CD25^{lo}Foxp3$^+$CD4$^+$ Tregs migrated into inflamed joint tissue, which began to produce IL-17, followed by promoted inflammation and local osteoclast activation [364].

Furthermore, IL-17$^+$Foxp3$^+$ Th17-like Tregs were also detected in the SF of RA patients. Patients with T1D *vs.* control subjects had comparable levels of peripheral blood CD4$^+$CD127$^{lo/-}$CD25$^+$ Tregs, whereas the percentage of Th1-like Tregs (Foxp3$^+$IFNγ^+) exceeded that in donor samples [365]. Moreover, 'naïve' Tregs exposed to IL-12 were able to upregulate the expression of several Th1-associated factors such as T-bet, CXCR3, and IFNγ. Similar data were obtained by Du *et al*. [366], who showed an increased level of circulating Th1-like Tregs, which expressed high levels of IFNγ and TNFα. The risk of developing T1D in children was also closely related to circulating memory effector Tregs-bearing chemokine receptors CCR6 and CXCR3, as well as the transcription factor GATA3 [367]. Children with T1D had a higher level of peripheral blood Th1-like (CCR6$^-$CXCR3$^+$) Tregs but a lower percentage of Th17-like (CCR6$^+$CXCR3$^-$) Tregs [368]. The mouse T1D model also demonstrated a hallmark role for Th1-like Tregs because T-bet$^+$Foxp3$^+$ T cells rather than Gata3$^+$Foxp3$^+$ cells were important in effective regulation of emerging autoimmune reactions in the islets of Langerhans [369].

Impaired thymic Treg differentiation was shown primarily in SLE and might profoundly affect relevant cell subset composition and functional properties both in peripheral tissues and in *in vitro* settings [370]. A decline in the level of circulating CD4$^+$CD25$^-$CD127$^{dim/-}$ Tregs was observed in SLE, so these cells exerted lower *in vitro* potential to suppress effector T cell proliferation, and they were also characterized by an increased level of apoptosis that correlated with disease activity [371]. It was shown that Foxp3$^+$Helios$^+$ Tregs in SLE patients expressed surface chemokine receptors CXCR3 and CCR4 at a level that insignificantly differed from that in the control group [372]. Also, some studies reported that SLE patients had an increased level of Th17-like Tregs able to produce IL-17 [373]. Moreover, mouse models revealed that the loss of Th17-like Tregs was accompanied by exacerbated pulmonary vasculitis, Th17 cell accumulation, and markedly higher mortality [374]. On the contrary, another *in vivo* study demonstrated that, at least in mice, Th17-like Tregs exhibited both protective and proinflammatory effects [375].

An experimental model of Sjögren's syndrome was associated with increased peripheral blood IFNγ-producing Th1-like Treg levels [376]. Moreover, NOD.B10.H2b mice (who spontaneously develop ocular surface disease upon aging) had a higher count of Foxp3$^+$IL-17$^+$ Th17-like or Foxp3$^+$IFNγ^+ Th1-like cells in the inflamed lacrimal gland and draining cervical lymph node [377], whereas patients with SS had an increased percentage of peripheral blood CD161$^+$CD25$^+$CD4$^+$ Th17-like Tregs characterized by decreased *in vitro* functional activity as well as downregulated foxp3 and helios expression [378].

Available publications assessing peripheral blood Treg percentage and absolute number in patients with AS are quite contradictory. For instance, some studies showed that circulating Treg levels in patients *vs.* control subjects did not differ significantly [178, 379,380], whereas others noted significantly decreased

CD4$^+$CD25$^+$FoxP3$^+$, CD4$^+$CD25$^+$CD127$^-$ [381] and CD4$^+$CD25^{high}CD127$^{low/-}$ Treg subsets [382]. In addition, Treg level was found to negatively correlate with BAS-DAI scores [383]. In connection with this, a role for individual Treg subsets, however, has not yet been thoroughly investigated.

A high level of Th1-like Tregs was found in intestinal lamina propria lesions during ulcerative colitis and Crohn's disease, implying that IFNγ^+T-bet$^+$ Tregs were involved in the underlying pathogenesis [384]. However, the data obtained in *in vivo* experimental models suggest both a positive and negative role for Th1-like Tregs related to their impaired anti-inflammatory properties upon migration into affected intestinal tissues [385,386]. Along with this, Ueno *et al*. [387] found a higher percentage of peripheral blood Th17-like Tregs (IL-17$^+$Foxp3$^+$CD4$^+$) in patients with Crohn's disease and patients with ulcerative colitis compared to the control group, so that *in vitro* experiments uncovered that such cells had lowered functional activity and were unable to effectively suppress effector T cell proliferation. Additionally, analyzing intestinal lesions revealed an increased level of IL-17$^{(+)}$ FoxP3$^{(+)}$ Th17-like Tregs in Crohn's disease *vs*. ulcerative colitis patients and the control group [388].

Relatively recently, it was shown that patients with IgG4-related disease had elevated levels of peripheral blood CD4$^+$CD25^{hi}CD127^{low}CD161$^+$ Th17-like Tregs that negatively correlated with serum C3 and C4 complement component concentrations [389]. Moreover, a high Treg infiltration level in inflamed tissue was observed in autoimmune pancreatitis, IgG4-related sclerosing cholangitis, and salivary gland tissues in Mikulicz disease [390].

In the case of sarcoidosis, a rise in the level of CXCR3-expressing Tregs—Th1-like and Th17.1-like Tregs—was shown, along with a decline in CXCR3$^-$CCR6$^+$ Th17-like Tregs among the total CD45RA-CCR7-effector memory Treg population [391]. Numerous studies point to increased concentrations of all three CXCR3 ligands, CXCL9 (MIG), CXCL10 (IP-10), and CXCL11 (I-TAC), both in serum [88,94,392] and BALF samples, where they are abundantly produced by alveolar macrophages [393,394], which may be a hallmark cue for Treg recruitment into the site of inflammation. Despite this, CXCR$^+$CCR6$^+$ Th17.1 cells dominated in BALF, whereas Treg levels were significantly lower than those in peripheral blood [253], potentially suggesting poor BALF Treg activity in suppressing inflammatory reactions in sarcoidosis.

In psoriasis, elevated phosphorylation of the transcription factor signal transducer and activator of transcription 3 (STAT3) was found in the circulating cells, which exerted a lowered potential to exhibit suppressive properties but produced large amounts of IFNγ, TNFα, and IL-17 [395]. Psoriatic plaques also contain Th17-like Tregs able to produce IL-17 [396]. Similarly, Bovenschen *et al*. [397] showed that patients with severe psoriasis had IL-17A$^+$, Foxp3$^+$, and CD4$^+$ T cells accumulated in the plaques. Moreover, *ex vivo* isolated Tregs from patients with severe psoriasis *vs*. control subjects were able to better differentiate into IL-17A-producing cells characterized by upregulated expression of RORγt and decreased Foxp3 level that was prominently potentiated after IL-23 exposure. These data were also confirmed in *in vivo* experimental animal models [398].

Decreased peripheral blood Treg levels were observed in patients with Graves' disease [399], which was further corroborated by molecular and biological study [400]. At the same time, the level of Tregs expressing surface CD69 activation markers in patient peripheral blood was increased, but their potential to suppress *in vitro* T cell proliferation was downmodulated [401]. Later, it was evidenced that Treg effector functions may be impaired [402]. which is also demonstrated in the meta-analysis by Chen *et al*. [403]. However, no experimental data on Treg subset composition is currently available.

The data indicates that CXCR3$^+$ Tregs provide an important role in inflammatory reactions and their regulation, especially in tissues rich in CXCR3 ligands. In the early stages of immunity, CXCR3 ligands attract large amounts of effector cells, which initiate inflammation and pathogen elimination. CXCR3$^+$ Tregs are not enough to suppress immunity. At the same time, when inflammation becomes chronic, there is an increase in the CXCR3$^+$ Treg population; such a tendency can play a role in compensation mechanisms. These cells can be potentially used as a marker for therapy efficacy. Unfortunately, at this point in time, data on the matter is still lacking.

7. CXCR3-Expressing CD8$^+$ T-Cell Subsets in Infections and Autoimmunity

Tc1 CD8$^+$ T lymphocytes like Th1 cells are essential in underlying type 1 inflammatory reactions, which is coupled to their prominent cytolytic properties mediated by perforin and granzymes stored in the cytosolic granules as well as the production of effector cytokines IFNγ and TNFα [195]. Tc1 CD8$^+$ T cells express surface CCR5 and CXCR3, whereas they lack other chemokine receptors specific to Tc2, Tc17, and follicular CD8$^+$ T lymphocytes (CCR4, CCR6, and CXCR5, respectively) [404]. In addition, CD3$^+$CD8$^+$IFNγ^+ Tc1 cells highly express IL-18R, which is also typical of Th1 cells solely found in the IFNγ-producing CD8$^+$ T cell subset [405]. On the other hand, Tc2 and Tc17 are also detected in the bloodstream, resembling Th2 and Th17, respectively, in terms of expressed transcription factors and secreted cytokines, but exerting no strong potential to destroy target cells [406]. A balance between the cytolytic Tc1, on the one hand, and the cytokine-producing Tc2 and Tc17 cell subsets, on the other hand, seems to play a crucial role in the emergence of diverse pathological conditions, including autoimmunity and infections. However, the data regarding a role for distinct

CD8$^+$ T cell subsets in the pathogenesis of such diseases remain extremely limited and require further evaluation.

7.1 CXCR3-Expressing CD8$^+$ T-Cell Subsets in Infections

Recently, we showed that peripheral blood Tc1 (CCR6$^-$CXCR3$^+$) CD8$^+$ T cell level was decreased in patients with tuberculosis, whereas that of CCR6$^-$CXCR3$^-$CD8$^+$ T cells significantly increased [407], which is in line with the data obtained by Ocaña-Guzmán et al. [408] describing decline in circulating CXCR3$^+$CD8$^+$ T cell level from untreated patients, but the therapy applied reversed the latter to normal range. In addition, patients with tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) infected with both Mtb and HIV showed a decreased percentage of CXCR3$^+$CD8$^+$ T cells [409]. Moreover, an inverse relation was found between 'naïve' CXCR3$^+$CD8$^+$ T cell level and the risk of developing TB-IRIS, whereas a higher percentage of CXCR3$^+$ effector CD8$^+$ T cells was closely related to the likelihood of developing TB-IRIS. It should be noted that a high level of serum CXCR3 ligands—MIG, IP-10, and I-TAC—was detected in TB patients [410]. Furthermore, biopsy immunohistochemistry examination detected CD8$^+$ T cells in alveolar walls and pulmonary cavities in pulmonary tuberculosis [411], which may be evidence of efficient CXCR3$^+$ cell migration into the site of inflammation. The Cxcr3$^{(-/-)}$ mouse strain also emphasized a crucial role for CXCR3$^+$CD8$^+$ T cells in defense against intracellular pathogens [412].

In COVID-19, it was shown that patients with acute disease had downregulated expression of Tc1 (CXCR3 and T-bet) and Tc17 (CD161 and CCR6), along with an upregulated level of Tc2 (CCR4 and GATA3) antigens in CD8$^+$ T cells [413]. The lack of circulating PD-L1$^+$CXCR3$^+$CD8$^+$ Teff cells is associated with a critical outcome in COVID-19, but convalescent vs. non-survivor patients contained elevated levels of PD-L1$^+$CXCR3$^+$CD8$^+$ cells [414]. On the contrary, another study showed that during severe SARS-CoV-2 infection, CD8$^+$ T cells highly expressed CCR6 and CXCR3 [415]. Moreover, the level of effector CD8$^+$ T cells with Tc17.1 CXCR3$^+$CCR6$^+$ phenotype and memory CXCR3$^-$CCR6$^+$CD8$^+$ T cells was increased in mild vs. severe COVID-19 patients [416]. In our study, we found a decline in CXCR3$^+$ Tc1 and CCR4$^+$ Tc2 CD8$^+$ T cells both in acute COVID-19 and patients 1-3 months later as compared to control subjects [49]. Of note, Yang et al. [417] also observed a lowered Tc1 cell level in convalescent patients compared to volunteers. Along with this, a higher level of CXCR3$^+$CCR6$^-$CD8$^+$ T cells (Tc1) was noted in adenoids from COVID-19 convalescent patients compared to the control group [418].

Viral persistence in HIV infection is related to diverse immune impairments, such as chronic low-grade inflammation, systemic immune activation, and depletion of T cells, including CD8$^+$ T cells [419,420]. Viral suppression and partial recovery of the immune response are usually achieved by highly active ART. However, spontaneous viral control without ART is observed in a very small cohort of HIV-infected patients called HIV controllers [421]. Various mechanisms, including protective MHC alleles and immune responses, particularly those mediated by CD8$^+$ T cells, are thought to be involved in HIV control. Good long-term CD8$^+$ T cell responses are necessary for spontaneous HIV control, which, despite this, may be altered by persistent viruses [422,423]. CXCR3 expression allows CD8$^+$ T cells to travel to the sites of inflammation, including the intestinal mucosa known to be affected by HIV infection [424]. In this regard, it was noted that a negative correlation between CXCR3$^+$CD8$^+$ T cell level and expression of mucosal CCL20 and CCL25 was identified. Asymptomatic HIV infection was coupled to CXCR3$^+$CD8$^+$ T cell levels accumulated in the peripheral blood and lymph nodes that were positively and inversely correlated with those of CD4$^+$ T cells and viral load, respectively [47].

It is also worth noting that levels of three CXCR3 ligands (especially CXCL10/IP10) change during HIV infection and are inversely correlated with disease progression [100]. Olivo et al. [425] assessed CXCR3 expression on memory CD8$^+$ cells in HIV-infected individuals and found that CXCR3-positive cells dominated among CM and EM CD8$^+$ T cell subsets. ART-treated patients were found to have a lower percentage of CXCR3$^+$ cells for EM cells than for CM cells. In contrast, the number of CXCR3$^+$ CM and CXCR3$^+$ EM CD8$^+$ T cells was comparable in volunteers and HIV controllers. Next, a question arose about whether HIV status and control type were associated with the percentage of CXCR3$^+$ cells in each of the memory CD8$^+$ T cell subsets. It was uncovered that the CM CD8+ T cell subset contained a higher percentage of CXCR3$^+$ cells in HIV-infected patients than in volunteers. In addition, HIV controllers but not ART-treated patients had a significantly higher percentage of the CXCR3$^+$ T cell subset among EM CD8$^+$ T cells compared to volunteers.

The chemokine receptor CXCR3 plays an essential role in the recruitment of Tc cells and the secretion of secondary type 1 cytokines (Tc1) in the liver. HCV may rely on immunoevasion by downmodulating CXCR3 expression. Larrubia et al. [426] showed that the level of liver CCR5/CXCR3-expressing CD8$^+$ cells was elevated and correlated with inflammation. Patients with chronic HCV infection had a count of peripheral blood CD8$^+$CCR5^{high}/CXCR3^{high} cells comparable with that in volunteers but a higher concentration of serum CXCL10/CCL3 chemokines. Interestingly, CXCR3 was preferentially expressed on HCV-specific CD8$^+$ T cells with central memory phenotype (CCR7$^+$CD45RO$^+$) in both acute and chronic phases of infection in blood [427]. Treatment with PEG-interferon α-2b in combination with ribavirin resulted in increased peripheral blood cell counts

and decreased serum CXCL10 and CCL3 concentrations. The rise in the number of CD8+CCR5^{high}/CXCR3^{high} cells at 24 weeks after treatment correlated with sustained virological response (SVR). Thus, antiviral treatment in chronic hepatitis C infection results in a higher number of CD8+CCR5^{high}/CXCR3^{high} cells associated with the Tc1 response and a decrease in relevant chemokine ligands. Achievement of viral control is associated with a treatment-related rise in the number of CXCR3-high-expressing CD8+ cells. On the other hand, HCV-infected subjects were found to contain a level of multifunctional peripheral blood Tc17 cells able to produce IL-10, IFNγ, or IL-21 along with IL-17A that negatively correlated with the magnitude of liver damage, whereas the level of monofunctional Tc17 cells positively correlated with liver damage [428]. Moreover, there has been a rise in the number of Tc17 cells as well as IFNγ-producing Tc17.1 cell was found in the liver of patients with chronic HCV infection and severe fibrosis compared with their peripheral blood counterparts [429].

7.2 CXCR3-Expressing CD8+ T-Cell Subsets in Autoimmunity

Patients with multiple sclerosis and neuromyelitis optica (NMO) at the active *vs.* remission stage were found to have elevated peripheral blood CD8+CXCR3+ and CD8+CCR4+ T cell levels, as well as a higher CD8+CXCR3+/CD8+CCR4+ ratio. Moreover, after being treated with IFNβ, the CD8+CXCR3+/CD8+CCR4+ ratio decreased significantly [430]. Moreover, total CXCR3+CD8+ T cells in MS patients had a higher percentage of cells expressing adhesion molecule $\alpha4\beta7^+$, accounting for migration into the GALT and facilitating entrance into intestinal tissue, Peyer's patches, and mesenteric lymph nodes [288]. It was also shown that peripheral blood Tc1 (CD8+IFNγ^+) and Tc17 (CD8+IL-17$^+$) cell levels increased in SPMS as well as at the relapse stage [431]. In addition, a series of studies noted an increased level of Tc17 cells in the CSF *vs.* peripheral blood samples in multiple sclerosis as well as compared with it in the CSF in the control group [432,433], so that Lolli *et al.* [434] also revealed a positive correlation between the CSF Tc17 percentage and the expanded disability status scale (EDSS). It is noteworthy that nervous tissue lesions were solely infiltrated by IFNγ-producing CD8+ T cells [435].

The level of surface CXCR3-expressing peripheral blood CD8+ T cells was significantly reduced in RA patients compared to the control group [161]. On the other hand, treatment of patients with TNFα inhibitors was accompanied by an increased level of peripheral blood CXCR3+CD8+ T cells 6 and 14 weeks after the onset of therapy [163]. Furthermore, CXCL9 and CXCL10 levels in RA patients were increased both in the serum and SF [72, 73], whereas patient peripheral blood-derived CD8+ T cells were able to migrate *in vitro* along a CXCL10 gradient that

was fully suppressed by using specific neutralizing antibodies [436]. Along with this, the SF from RA patients was revealed to contain a higher level of IFNγ^+CD3+CD8+ cells as well as CD8+ cells enriched in effector molecules such as perforin, granzymes, and granulysins [437]. Taken together, these data point to an essential role played by effector Tc1 CD8+ T cells in RA pathogenesis as well as by CXCR3 ligands in the recruitment of such cells to the site of inflammation.

A role for CD8+ T cells in SLE pathogenesis remains understudied. However, the impact of such cells in inflammatory reactions is highlighted by the data about increased circulating blood CD8+ T cell levels positive for proliferation marker Ki-67, which indicates an intensive clonal expansion occurring in the peripheral lymphoid organs, which could also become a predictor of low therapeutic effectiveness [438]. Moreover, the level of circulating mature effector CD8+ T cells was correlated with the SLE Disease Activity Index score [439,440]. Patients with SLE had an increased level of peripheral blood CXCR3+CD8+ T cells [441]. On the other hand, a higher percentage of circulating Tc17 cells was found in SLE, but no relation to clinical parameters was described [442].

Distinct CD8+ T cell subsets play an important role in the pathogenesis of Sjögren's disease [443]. For instance, a decline in the level of circulating CXCR3+CD8+ T cells was noted in Sjögren's disease, and its peripheral blood level was correlated with disease severity as well as rheumatoid factor concentrations and Schirmer test data [444]. Moreover, Sjögren's disease, modeled in Gal1-null mutant *vs.* wild-type mice, highly expressed CXCL9 and CXCL10 in the submandibular glands and was found to have strong CXCR3+CD8+ T cell infiltration in the salivary gland tissue [445]. Along with this, non-obese diabetic (NOD) mice were allowed to demonstrate the effectiveness of anti-CXCR3 antibodies in protecting salivary gland tissues from CXCR3+CD8+ T cell-mediated damage [446]. A study by Gao *et al.* [447] showed that CD69+CD103+CD8+ T cells effectively infiltrate salivary gland tissue in a mouse SS model, whereas *IFNγ* gene knockout was able to not only lower the level of CD8+ T cell infiltration into salivary gland tissue and its damage, promote the recovery of salivary acini and secretory function, but also exhibit a protective effect in manifested SS, even in the case of repeated disease induction. Hence, these data indicate that Tc1 CD8+ T cells play an important role in the pathogenesis of Sjögren's disease, which may be potentially used as a therapeutic target.

Tc1 cells, which produce IFNγ, IL-2, and TNFα, are believed to play an important role in the pathogenesis of psoriasis [448]. At the same time, Tc17 cells producing both Tc1 cytokines, including TNFα and IFNγ, and IL-17, IL-21, and IL-22 were found in skin lesions, which indicates that they acquired the properties of CXCR3+CCR6+ Tc17.1 cells [449,450]. In addition, patient skin lesions

Table 2. CXCR3-expressing T cell subsets in infections and autoimmunity.

	Th1	Th17.1	Tfh1	Treg1	Tc1
Tuberculosis (TB)	↑[139,140,143]	↓[205,208–210] ↑[206,211]	↓[210]		↓[407,408]
COVID-19	↑[131,134]	↓[131,202]	↑[135] ↓[202]	↑[344]	↓[49,417]
Human Immunodeficiency Virus (HIV)		↓[215,216]	↑[281]	↑[349,350]	
Hepatitis C Virus (HCV)	↑[153]	↓[218] ↑[219]	↑[285]		↑[426] =[427]
Multiple Sclerosis (MS) (blood)	↑[160]	↑[222] ↓[224]	↓[286] ↑[288,289]	↓[358]	↑[430,431]
MS (liquor)	↑[156]	↑[223,224]	↑[290]	↑[341]	
Rheumatoid Arthritis (RA) (blood)	↓[108,161,162]	↓[226,232]	=[296]	↓[337] ↑[361]	↓[161]
RA (synovial fluid)	↑[161]	↑[72]		↑[361]	↑[437]
Type 1 Diabetes (T1D)	↓[164,165]	↓[233]	=[298]	↑[365,366]	
Systemic Lupus Erythematosus (SLE)	↑[169]	↑[234,235]	↓[299] ↑[171]		↑[441]
Primary Sjögren's syndrome (pSS)	↓[174]	↑[236]	↓[305]		↓[444]
Ankylosing Spondilitis (AS)	↑[178,179]	↑[240,241]	↑[310] ↓[311,312]		
Inflammatory Bowel Disease (IBD)	↓[182]	↑[199,244,245]	↑[314]	↑[385]	↑[458]
Sarcoidosis (blood and bronchoalveolar lavage fluid (BALF))	↓[186] ↑[188]	↑[248,250–252] ↓[253]	↓[319]	↑[391]	↓[453] ↑[455]
Psoriasis (blood and skin)	↓[190]	↑[259]	↓[323,324]		
Graves' disease	↓[168]		↓[326]		

Note: Th1, T helper cells 1; Th17.1, T helper cells 17.1; Tfh1, T follicular helper cells 1; Treg1, T regulatory cells 1; Tc1, T cytotoxic cells 1; ↓ indicates decreased levels of circulating cells; ↑ signifies increased levels; = indicates that the level of circulating cells remains unchanged.

contained higher levels of IL-17A and IL-22-producing Tc17 and Tc22 cells, respectively, which are actively involved in psoriatic plaque inflammation [451]. At the same time, peripheral blood Tc17 cell levels in patients with psoriasis solely correlate with clinical disease severity [452]. Therapeutic blockade of IL-17 was accompanied by a decreased level of CCR6$^-$CXCR3$^+$ Tc1 lymphocytes in psoriasis patients [259].

Before stimulation with phorbol ester and ionomycin, BALF and sputum samples from patients with sarcoidosis contained a significantly lower number of IFNγ^+CD8$^+$ T cells than in donors [453]. The inter-group level of BALF or sputum IL-4-secreting CD8$^+$ T cells did not differ significantly. Nor were they observed post-stimulation in both sample types while comparing patients with sarcoidosis and control subjects. However, CD8$^+$ T cell perforin expression in all samples tested was significantly downmodulated in patients with sarcoidosis. Surface adhesion molecule (CD62L, CD71) expression level was significantly higher on CD8$^+$ T cells post-stimulation both in BALF and sputum samples collected from sarcoidosis patients *vs.* the control group [453]. Expression of BALF *vs.* peripheral blood CD8$^+$ T cell surface CXCR3 was significantly higher in sarcoidosis, whereas the IL-12R level was elevated only in

BALF. Patients with Löfgren's syndrome had an increased number of CCR4-expressing CD8$^+$ T cells [454]. When comparing the general sarcoidosis group (including subjects with and without Löfgren's syndrome) with the control group, an increased level of peripheral blood CD8$^+$ grzB$^+$ and CD8$^+$ perforin$^+$ T cells was found in sarcoidosis [455].

Early studies with animal models suggested that Tc1 cells play a prominent role in IBD pathogenesis [456,457], which was partly confirmed by Funderburg *et al.* [458], who assessed patients with ulcerative colitis with elevated peripheral blood IFNγ^+ Tc1 levels that correlated with those of serum inflammation markers such as IL-6 and CRP. A relation was also found between Tc1 cell level and fistula as well as ulcer formation in patients with Crohn's disease [459], paralleled by evidence that in active IBD perforin-positive effector Tc1 cells solely and actively infiltrate intestinal mucosa lesions [460].

On the other hand, inflamed bowel tissue samples from ulcerative colitis *vs.* Crohn's disease patients and control subjects were shown to contain a lower percentage of Tc17 in the lamina propria [461], whereas in both patient groups, its peripheral blood counterpart was elevated compared to the control group. Similarly, Globig *et al.* [462]
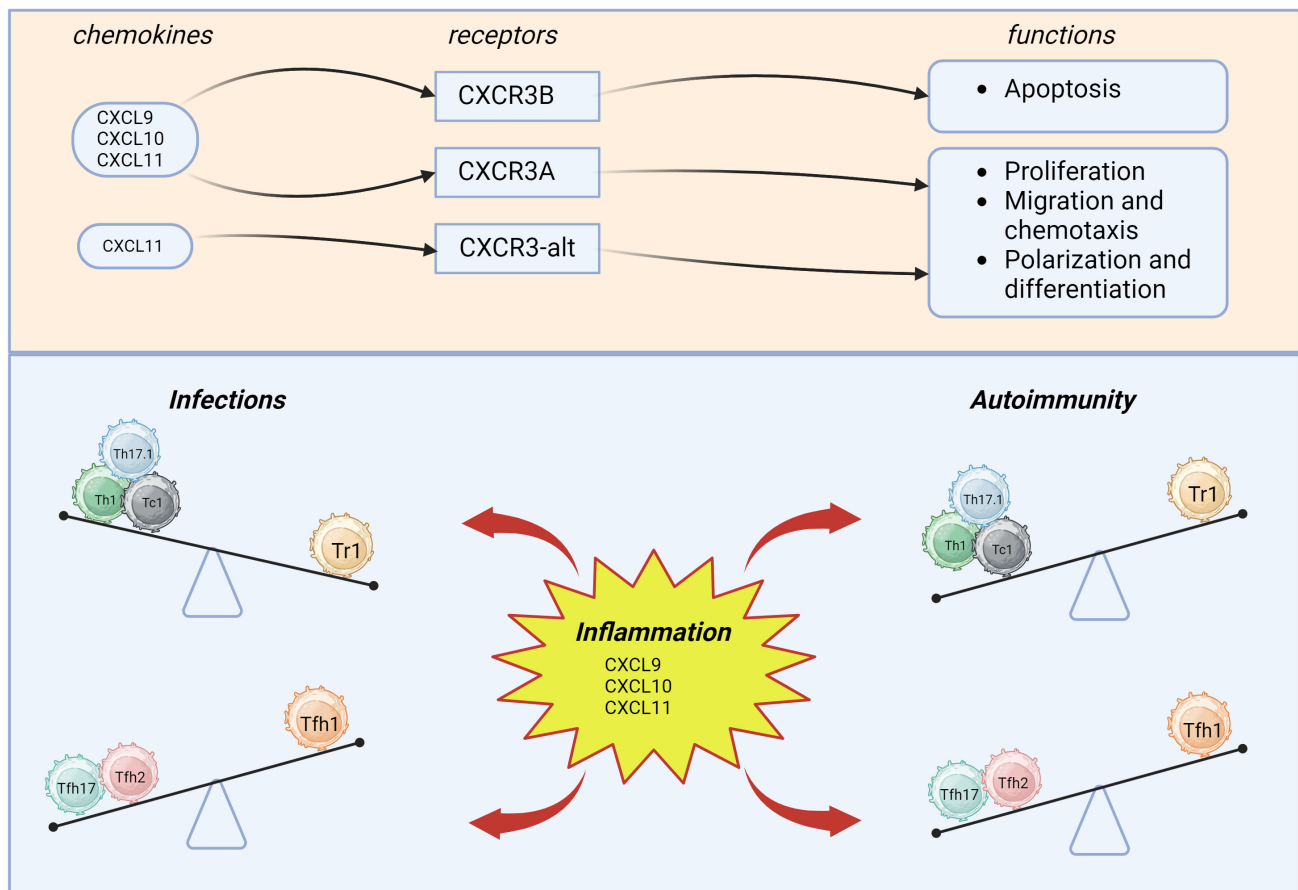
Fig. 2. CXCR3 and their chemokines in T cell function and pathology. Created with BioRender.com.

revealed increased Tc17 levels in the peripheral blood and intestinal tissues of patients with active Crohn's disease. While analyzing colon biopsy specimens from patients with ulcerative colitis, there was a strong infiltration of Tc17 cells, which could primarily produce IL-17 in the inflamed tissue [463]. Additionally, developing IBD-related inflammation was solely associated with Tc17 cells by using animal models that also involved IL-17- and IFNγ-producing Tc17.1 cells [464]. It should also be noted that Tc17 cells may produce key cytokines (IL-17 and IL-22), accounting for not only inflammation but also the onset of intestinal mucosa repair and regeneration [465]. Hence, a deeper insight into a role for this cell type may be gained from further investigations.

Thus, along with thoroughly described Tc1 CD8$^+$ T cells able to produce IFNγ and TNFα and exert cytolytic properties, other cytokine-secreting CD8$^+$ T cell subsets are found in the circulation and peripheral tissues. Moreover, Tc2 and Tc17 cells, via immunoregulatory cytokines, are actively involved in the formation of the microenvironment during physiological and pathological processes. Owing to such properties, Tc2 and Tc17 cells profoundly affect both adaptive CD4$^+$ T cells and effector innate cells at the site of inflammation. Further studies aimed at characterizing fine crosstalk between all such CD8$^+$ T cell subsets may

provide deeper insights into the physiological significance of the balance between them that may be applied both in the diagnostics of autoimmune and infectious processes and in the search for new therapeutic opportunities for modulating the overall immune response.

The overall dynamics of changes in CXCR3$^+$ T cells in infectious and autoimmune diseases are presented in Table 2 (ref. [49,72,108,131,134,135,139,140,143,153,156, 160–162,164,165,168,169,171,174,178,179,182,186,188, 190,199,202,205,206,208–211,215,216,218,219,222– 224,226,232–236,240,241,244,245,248,250– 253,259,281,285,286,288–290,296,298,299,305,310– 312,314,319,323,324,326,337,341,344,349,350,358,361, 365,366,385,391,407,408,417,426,427,430,431,437,441, 444,453,455,458]).

8. Conclusions and Future Perspectives

In recent years, new data on the CXCR3/CXCL9-11 axis has emerged. All studies dedicated to autoimmunity and infection highlight the importance of CXCL9, CXCL10, and CXCL11 for the attraction of CXCR3$^+$ T cells to an inflammatory site.

With some hesitation, it might be possible to divide CXCR3$^+$ T cell subsets into so-called 'pro-inflammatory' cells (Th1, Th17.1, and Tc1) and 'regulatory' cells (Tfh1

and Treg1). The balance between these two types of cells seems to be crucial in pathogen elimination in infectious diseases; it is also important for tissue repair. However, when pathogen elimination is impossible (for instance, in TB infection, HIV infection, or HCV infection), the 'pro-inflammatory' population plays a key role in tissue damage, leading to chronic inflammation. In autoimmunity, when autoreactive $CXCR3^+$ T cells accumulate in tissue, it causes the attraction of effector cells and stimulation of chronic inflammation. These processes are mediated by IFNγ-producing cells (Th1, Th17.1, and Tc1) that stimulate the production of IFNγ-inducible ligands in inflammatory site cells, which leads to the attraction of more $CXCR3^+$ T cells and the formation of a CXCR3-dependent amplification loop. The dysfunction of $CXCR3^+$ Tregs can contribute to the loop, but it makes the drugs targeted against CXCR3 ligands quite effective (Fig. 2).

A perspective on developing drugs therapeutically targeting CXCR3 and its ligands can be highly relevant for a wide range of autoimmune pathologies, such as rheumatoid arthritis, multiple sclerosis, Crohn's disease, sarcoidosis, psoriasis, and type 1 diabetes. This kind of medications may block the migration of diverse CXCR3-expressing cells to the site of autoimmune inflammation. Multiple cell types expressing this chemokine receptor play an essential role in the pathogenesis of autoimmune diseases, as demonstrated in previous sections of the current review. Furthermore, understanding the role of CXCR3 and its ligands might make these molecules as targets for therapeutic intervention in a wide range of diseases.

Moreover, CXCR3-targeted therapy may act simultaneously on several cell subpopulations, providing a rather advantageous solution in the context of suppressing autoimmune inflammation in pathologies where several $CXCR3^+$ T cell subsets play an underlying role in the pathogenesis. Currently, no data on clinically used CXCR3 antagonists in patients with autoimmune diseases is available. However, there are very promising experimental studies based on applying such drugs to animal models. For instance, AMG487, a selective CXCR3 antagonist, alleviated the magnitude of clinical parameters and histological inflammatory lesions in a mouse collagen-induced arthritis (CIA) model [466]. This investigational drug downregulated the expression of T-bet, IL-17A, RORgt, and IL-22 but increased the levels of Foxp3 and IL-10 in immune cells. AMG487 decreased Th1, Th17, and Th22 cells in parallel with an elevated Treg level at the site of inflammation [466,467]. Another CXCR3-specific antagonist, NBI-74330, also reduced the arthritis severity score and improved the histological picture of the inflammatory lesion in mouse collagen-induced arthritis.

In this regard, a decline in $CD4^+IFN\gamma^+$, $CD4^+$T-bet$^+$, $CXCR3^+IFN\gamma^+$, $CXCR3^+TNF\alpha^+$, $CXCR3^+$T-bet$^+$, $CD4^+RANKL^+$, $CD4^+IL$-17A$^+$, $CD4^+RORgt^+$ cells along with IFNγ, TNFα, T-bet, RANKL, IL-17A,

RORgt, and IL-22 mRNA levels were found in the lesion [468]. Some drugs were tested *in vitro* on human peripheral blood cells, and the investigational drug SCH 546738 was found to bind with high affinity to the human CXCR3 receptor [469]. Apart from this, SCH 546738 is able to displace CXCL10 and CXCL11 from the cognate binding site of human CXCR3. Also, *in vitro* experiments demonstrated that SCH 546738 effectively and specifically inhibited CXCR3-mediated chemotaxis of activated human T cells [469].

The mouse collagen induced arthritis (CIA) model revealed that SCH 546738 slowed disease progression as well as markedly decreased disease severity in rat and mouse Experimental autoimmune encephalomyelitis (EAE) models [469]. A mouse model of pulmonary granulomatosis showed that the CXCR3/CCCR5 dual blocker TAK-779 resulted in a lower number of BALF $CXCR3^+CD4^+$ and $CCR5^+CD4^+$ T cells as well as an improved disease course [470]. Hence, such data suggests a potential benefit from using this drug in granulomatous autoimmune diseases such as sarcoidosis and CD. AMG487 was also examined in mouse diabetic retinopathy, demonstrating that it prevented early eye damage [471]. Recently, the U.S. Food and Drug Administration (FDA) approved an anti-CD3 monoclonal antibody for the prevention and retardation of the progression of type 1 diabetes [472]. Christen *et al*. [473] assessed the effectiveness of using an anti-CD3 antibody in combination with the new low-molecular-weight CXCR3 antagonist ACT-777991. It was found out that the anti-CD3/ACT-777991 therapy persistently reduced blood glucose levels, which resulted in a higher rate of disease remission compared with either monotherapy [473]. Thus, therapy targeting the CXCR3/CXCL9, CXCL10, and CXCL11-axes is a fairly promising approach for molecular pharmacology and may be the key to preventing the development and progression of multiple autoimmune diseases.

Abbreviations

ACPAs, anti-citrullinated protein antibodies; ANCA, antineutrophil cytoplasmic antibody; anti-AChR, anti-acetylcholine receptor; anti-CCP, anti-cyclic citrullinated peptides; anti-MCV, anti-mutated citrullinated vimentin; ARDS, acute respiratory distress syndrome; ART, antiretroviral therapy; AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease activity score; BALF, bronchoalveolar lavage fluid; BASDAI, Bath AS Disease Activity Index; BBB, blood-brain barrier; CD, Crohn's disease; CDAI, Clinical Disease Activity Index; CIA, collagen-induced arthritis; CM, central memory; CRP, C-reactive protein; CSF, cerebrospinal fluid; DAS28, Disease Activity Score in 28 joints; DCTDs, diffuse connective tissue diseases; DTH, delayed-type hypersensitivity; EAE, experimental autoimmune encephalomyelitis; EDSS, expanded disability status scale; EM, effector memory; ESR, erythrocyte sedimentation rate; ESSDAI, EULAR Sjogren's Syndrome Disease Activity Index; GALT, gut-

associated lymphoid tissue; GC-Tfh, germinal center follicular Th cells; HIV, human immunodeficiency virus; LTBI, latent tuberculosis infection; MS, multiple sclerosis; NMO, neuromyelitis optica; PASI, Psoriasis Area and Severity Index; PPMS, primary progressive multiple sclerosis; RA, rheumatoid arthritis; RRMS, relapsing-remitting multiple sclerosis; SF, synovial fluid; SIV, simian immunodeficiency virus; SJC, swollen joint counts; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; SPMS, secondary progressive multiple sclerosis; SS, Sjogren's syndrome; T1D, type 1 diabetes; TB, pulmonary tuberculosis; TB-IRIS, tuberculosis-associated immune reconstitution inflammatory syndrome; TCR, T cell receptor; TEMRA, terminal effector memory T cells re-expresses CD45RA; TJC, tender joint counts; TRM, tissue-resident memory cells; TSCM, stem-like memory T cells.

Author Contributions

AR, IK and AT designed the work. AR, IK, NA, ZK and DI investigated it. AR, IK and NA prepared the charts. AR, IK, NA, ZK, DI and AT wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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