


Review

Mucosal Immunity and Autoimmune Diseases: New Perspectives From Mechanisms to Treatment

Hai-Fen Wei^{1,2}, Harry Asena Musonye^{1,2}, Sha-Sha Tao^{1,2,3,*}, Hai-Feng Pan^{1,2,*} ¹Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, 230032 Hefei, Anhui, China²Inflammation and Immune Mediated Diseases Laboratory of Anhui Province, 230032 Hefei, Anhui, China³Preventive Medicine Experimental Teaching Center, School of Public Health, Anhui Medical University, 230032 Hefei, Anhui, China*Correspondence: taoshasha@ahmu.edu.cn (Sha-Sha Tao); panhaifeng@ahmu.edu.cn (Hai-Feng Pan)

Academic Editor: Arianna Di Stadio

Submitted: 4 December 2025 Revised: 20 January 2026 Accepted: 2 February 2026 Published: 16 April 2026

Abstract

Autoimmune diseases (ADs) impose a significant and growing burden on global health. Emerging studies indicate that dysregulation of the mucosal immunity is not merely a consequence of disease progression but often represents a critical sentinel event that triggers autoimmune responses. This review explores a paradigm shift in the understanding of ADs pathogenesis, moving away from an exclusive emphasis on systemic immune imbalance towards a perspective centered on mucosal immune abnormalities characterized by mucosal barrier dysfunction and microbiota dysbiosis. We synthesize the principal mechanisms through which mucosal immunity contributes to the onset and progression of ADs and critically evaluate emerging therapeutic strategies. These insights offer new opportunities for precision medicine approaches that intervene at the mucosal origins of ADs.

Keywords: autoimmune diseases; immune mechanisms; targeted therapy; microbiota; gut-kidney axis; mucosal immunity

1. Introduction

Autoimmune diseases (ADs) are a group of disorders caused by pathological immune responses in which B cells and T cells react against self-antigens, leading to the targeting and destruction of normal tissues. The etiology of these diseases remains unclear. However, their global incidence is increasing, affecting about 4% of the population, especially women, and imposing a complex and chronic burden on healthcare systems globally [1]. Mucosal immunity refers to localized immune responses that occur within mucosal tissues, which includes the gastrointestinal, respiratory, and urogenital tracts, as well as the oral cavity. These tissues constitute the body's first line of defense against external pathogens [2]. Traditional research on the pathogenesis and treatment strategies for ADs has primarily focused on systemic immune dysregulation and global immune suppression. However, recent studies are driving a paradigm shift in this understanding. An increasing body of evidence suggests that dysfunction of the mucosal immune system, distributed across the gut, respiratory tract, oral cavity, and urinary tract, often serves as a common precursor and driving factor in the occurrence and progression of ADs [3,4]. Immunoglobulin A nephropathy (IgAN) is a typical representative of the mucosal-systemic axis pathogenic mechanism, and its onset is associated with dysregulation of the mucosal immune system in multiple sites. This realization expands the focus of ADs research from mere systemic immune suppression to a deeper understanding and precise regulation of immune homeostasis at the mucosal level. Accordingly, this review aims to systematically elaborate on

the core mechanisms of mucosal immune dysregulation in ADs by analyzing both shared and site-specific pathological pathways in key mucosal sites. Notably, we emphasize emerging therapeutic strategies targeting mucosal immunity, including the restoration of microbial homeostasis, localized immune modulation, and precision-targeted interventions. Together, these approaches provide a new theoretical framework and potential intervention strategies for the precise prevention and treatment of ADs.

2. Overview of the Mucosal Immunity

Mucosal immunity encompasses the localized immune responses that occur within mucosal tissues, including the respiratory, gastrointestinal, oral, and urogenital tracts [2]. This system depends on the synergistic coordination between innate and adaptive defense mechanisms. The innate immune system is formed by the mucosal epithelial layer together with its associated physical, chemical, and biological barriers. Within this framework, the physical barrier is primarily composed of secretory mucus and epithelial tight junctions. Furthermore, distinct mucosal sites possess specialised clearance mechanisms [5]. For example, ciliated cells in the respiratory tract facilitate the expulsion of mucus and foreign particulates through coordinated ciliary beating, while the intestinal tract utilizes peristalsis and rapid epithelial cell turnover to substantially reduce the risk of pathogen colonization [6,7]. Adaptive immunity, characterized by antigen specificity and immunological memory, is largely mediated by mucosa-associated lymphoid tissue (MALT), which can be functionally divided



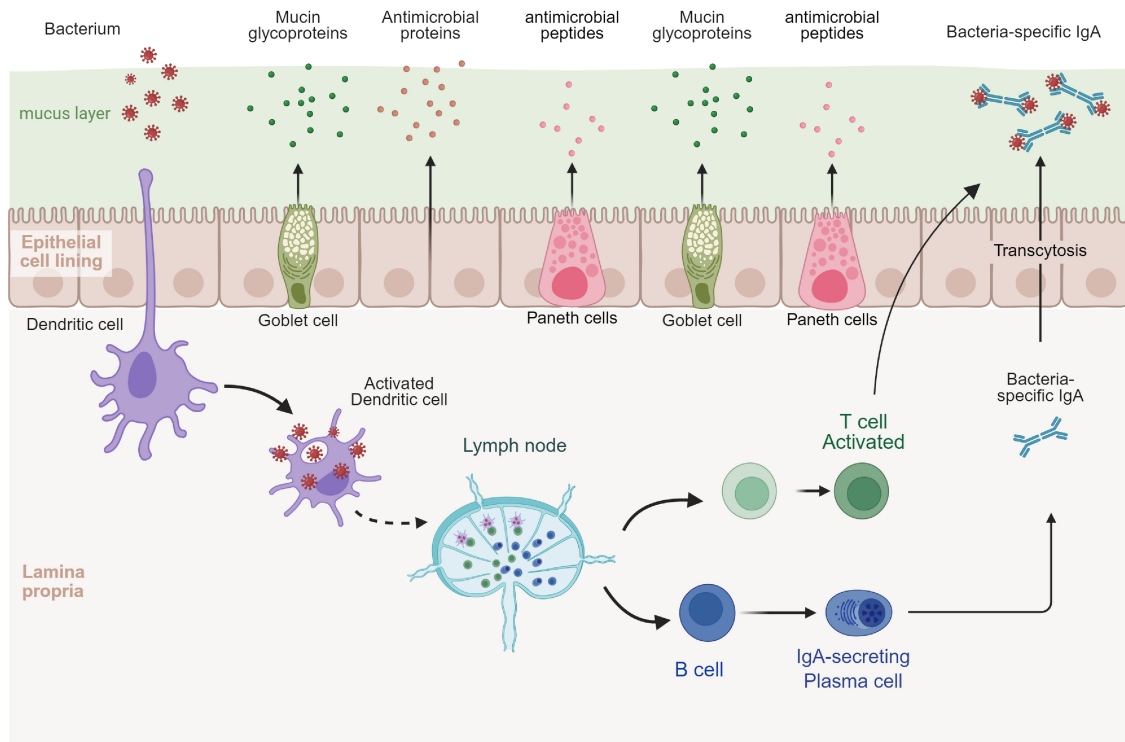


Fig. 1. Immune mechanisms of the intestinal mucosa. Notes: IgA, immunoglobulin A. This figure was created using BioRender.com (<https://www.biorender.com/>).

into inductive sites and effector sites [8]. Inductive sites are responsible for initiating antigen-specific T cell and B cell responses. Effector sites such as the epithelium and the lamina propria execute the downstream defensive functions [4]. This section illustrates the specific mechanism of mucosal immunity using the intestinal mucosa as an example (Fig. 1). Epithelial cells, antimicrobial peptides, and mucins secreted by goblet cells form a physical and chemical barrier. Once this barrier is breached, dendritic cells (DCs) activate antigen-specific T cells and assist B cells in differentiating into plasma cells. The immunoglobulin A (IgA) secreted by these plasma cells then travels through the epithelium into the intestinal lumen to coat pathogens for immune clearance, which ultimately maintains intestinal homeostasis [9,10].

3. Intestinal Mucosal Immunity and ADs

The pathophysiology of ADs is related to intestinal mucosal immunity. The underlying mechanisms include dysbiosis of the intestinal microbiota, impaired intestinal barrier function, and abnormal activation of local immune cells in the intestine. In this section, we clarify how intestinal mucosal immune responses contribute to, and regulate the occurrence and progression of ADs.

3.1 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by persistent inflamma-

tory response and immune-mediated tissue damage, which can involve multiple organ systems such as the skin, mucosa, musculoskeletal, blood and kidney [11]. Patients with SLE often exhibit gut microbiota dysbiosis, manifested in the alterations in the Firmicutes-to-Bacteroidetes ratio, increased pro-inflammatory bacteria (i.e., *Streptococcus*), and reduced anti-inflammatory species belonging to *Bifidobacterium* [12]. Katsushima *et al.* [13] found that gut bacteria-derived adenosine triphosphate (ATP)-binding cassette (ABC) transporters can serve as cross-reactive antigens, inducing the production of anti-dsDNA antibodies. This highlights the crucial role of bacterial translocation and molecular mimicry in driving the autoimmune response in SLE. Additionally, increased intestinal permeability, marked by elevated levels of zonulin, has been found to correlate with disease activity in SLE patients [14].

3.2 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disease primarily characterized by invasive synovitis. Clinically, it commonly presents as symmetric polyarthritis with joint pain, swelling, and morning stiffness, and can progressively lead to irreversible destruction of articular cartilage and bone [15]. Impairment of the intestinal mucosal barrier is regarded as an early event in RA pathogenesis. A study has shown that abnormalities in intestinal permeability are present before the onset of overt clinical symptoms of arthritis. Consistent with this, animal

experiments have demonstrated that mice with collagen-induced arthritis (CIA) exhibit early-stage gut microbiota dysbiosis and intestinal mucosal inflammation [16]. These changes may be associated with aberrant activation of signalling pathways involving intestinal tight junction proteins [17]. In addition, the gut microbiota may play an important role in the initiation and maintenance of systemic inflammation in RA. For instance, *Prevotella copri* promotes the expression of interleukin-17 (IL-17) and T helper 17 (Th17)-related cytokines, thereby exacerbating disease progression [18]. Conversely, *Parabacteroides distasonis* has been shown to alleviate arthritis symptoms, potentially through modulation of bile acid metabolism [19].

3.3 Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic, recurrent immune-mediated disorder that includes Crohn's disease (CD) and ulcerative colitis (UC). Its main clinical manifestations are abdominal pain, diarrhea, bloody stools and weight loss [20]. Beneficial commensal bacteria, such as *Faecalibacterium prausnitzii* and *Roseburia* species, are essential for maintaining intestinal homeostasis and alleviating inflammatory symptoms. In contrast, the proliferation of pathobionts, including *Escherichia coli* and *Clostridium difficile*, is associated with disease exacerbation and more severe clinical manifestations [21]. Notably, the impairment of intestinal barrier integrity represents a critical pathogenic element of IBD. This impairment arises from multiple mechanisms, including epithelial cell death, abnormalities in intercellular tight junctions, dysfunction of the mucus layer, and dysbiosis of the symbiotic microbiota, collectively contributing to sustained intestinal inflammation [22].

3.4 Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is a T-cell-mediated autoimmune disease characterized by progressive destruction of pancreatic β cells, resulting in absolute insulin deficiency. Patients rely on exogenous insulin to maintain stable blood sugar levels [23]. Compared with healthy individuals, patients with T1DM exhibit significant alterations in gut microbiota composition, characterised by an increased abundance of taxa such as *Escherichia-Shigella*, *Veillonella atypica*, and *Clostridium clostridioforme*, alongside a marked reduction in beneficial symbionts, including *Bifidobacterium*, *Bacteroides*, and *Streptococcus oligofermentans*. Further analysis reveals that these depleted commensal groups are positively correlated with levels of metabolites associated with anti-inflammation and energy metabolism, whereas the microbiota enriched in T1DM are linked to metabolites involved in oxidative stress and immune activation [24]. A cohort study has also confirmed that the rate of T1DM progression is closely associated with fluctuations in the abundance of various intestinal bacteria [25]. Notably, gut microbiota dysbiosis leads to a reduction in the production of

short-chain fatty acids (SCFAs), which in turn diminishes the secretion of glucagon-like peptide-1 (GLP-1) and exacerbates inflammatory responses. This cascade of changes can inhibit insulin secretion and damage pancreatic β -cells, thereby increasing the risk of developing T1DM [26].

3.5 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by immune-mediated demyelination, neurodegeneration, and progressive functional disability [27]. In recent years, the gut-brain axis has attracted considerable attention as a pivotal pathway linking intestinal health with neurological wellbeing. Studies have shown that MS patients frequently exhibit significant alterations in gut microbiota composition [28]. Notably, Gargano *et al.* [29] discovered that dysbiosis of the intestinal fungal community triggers the activation of mucosal-associated invariant T (MAIT) cells. These activated cells subsequently cross the blood-brain barrier, infiltrate the central nervous system, and secrete pro-inflammatory cytokines, thereby directly contributing to and exacerbating the neuroinflammatory process in MS. Furthermore, gut dysbiosis influences the production of microbial metabolites, including various secreted molecules, membrane components, neurotransmitters, and hormone-like substances. These signalling molecules can modulate central nervous system functions by regulating immune and inflammatory responses, playing a crucial regulatory role in the pathophysiology of MS [30].

3.6 Immunoglobulin A Nephropathy

IgAN is the most common type of glomerulonephritis driven by an autoimmune response against galactose-deficient immunoglobulin A1 (Gd-IgA1) [31]. Compared with healthy individuals, patients with IgAN exhibit alterations in both the diversity and composition of the gut microbiota. These changes are correlated with clinical indicators such as estimated glomerular filtration rate (eGFR) and urine albumin-creatinine ratio (UACR), suggesting a link between intestinal dysbiosis and disease severity [32]. Gut dysbiosis may exacerbate the overproduction of pathogenic Gd-IgA1 by activating toll-like receptor 4 (TLR4) signalling pathway and promoting the expression of B-cell-activating factor (BAFF) [33]. Recent research has further revealed that the deficiency of the polypeptide N-acetylgalactosaminyltransferase 14 (GalNAc-T14) leads to aberrant O-glycosylation of intestinal mucins. This disruption interferes with the normal homing of B cells to mucosal sites, ultimately resulting in the large-scale entry of pathogenic Gd-IgA1 into the systemic circulation, where they form immune complexes that deposit in the kidneys [34]. These findings highlight the central role of the gut-kidney axis in the pathogenesis of IgAN.

3.7 Autoimmune Thyroid Disease

Autoimmune thyroid disease (AITD) is an organ-specific autoimmune disorder that involves complex interactions among different components of thyroid tissue. Based on clinical outcomes and immune phenotypes, it can be categorized into two main types, Hashimoto's thyroiditis (HT) and Graves' disease (GD) [35]. Intestinal mucosal immunity may play a role in the inflammatory induction process of AITD. Specifically, the impairment of intestinal barrier integrity can lead to dysbiosis, resulting in a decrease in beneficial metabolic products such as SCFAs alongside increased exposure to harmful substances. These changes can ultimately promote excessive production of pro-inflammatory cytokines [36]. Furthermore, structural similarities between protein sequences in *Lactobacillus* and *Bifidobacterium* and thyroid autoantigens (peroxidase and thyroglobulin), may influence immune responses through molecular mimicry [37].

Gut mucosal immunity plays a dual role as both an amplifier and a regulator in ADs. Local barrier dysfunction and dysbiosis form a common pathogenic foundation, while specific microorganisms, metabolic products, or immune pathways interact with host genetic susceptibility to determine the specific target organs and clinical phenotypes of the autoimmune response. This provides a unified framework for understanding the common pathological basis of ADs and their individualized clinical manifestations. It also suggests that while restoring the integrity of the gut barrier is a universally applicable strategy, personalized management for different ADs still requires precise regulation of specific microbial strains and their metabolic products.

4. Respiratory Mucosal Immunity and ADs

In addition to the gut, the respiratory mucosal immune system serves as a primary interface between the body and the external environment. Beyond serving as a physical barrier against pathogens, it plays a crucial role in the pathogenesis of ADs as discussed in this section.

4.1 Rheumatoid Arthritis

During the high-risk period and early stages of RA, abnormal T cell-driven activation of B cells has been detected within the lung mucosa of patients, accompanied by high-frequency of somatic mutations and antibody class transitions. These processes facilitate the generation of citrulline-reactive autoantibodies [38]. This evidence supports the concept that the respiratory mucosa may serve as an important starting site for the autoimmune response of RA. Meanwhile, RA patients frequently exhibit mucosal dysbiosis, with the abundance of specific microbial taxa being correlated with anti-cyclic citrullinated peptide (anti-CCP) antibody levels, as well as various disease markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [39]. Furthermore, in both individuals at high risk of RA and patients, neutrophils in the lungs are more

prone to undergoing neutrophil extracellular trap formation (NETosis), thereby releasing a substantial array of citrullinated autoantigens [40], further underscoring the pivotal role of the local respiratory immune microenvironment in the pathogenesis of RA.

4.2 Immunoglobulin A Nephropathy

Respiratory mucosal immune dysregulation may directly contribute to the pathogenesis of IgAN through alterations in microbial structure and the aberrant activation of associated signalling pathways. A study has demonstrated that the respiratory microbiota in IgAN patients undergoes significant shifts, specifically characterised by an increased abundance of genera such as *Neisseria* and *Streptococcus*, alongside a reduction in *Prevotella*. Notably, immunosuppressive therapy has been shown to reduce the levels of *Neisseria* and *Actinobacillus* [41]. Kano *et al.* [42] found that the continuously activated toll-like receptor 9 (TLR9) signalling pathway can up-regulate the expression of key factors of B cells such as BAFF and a proliferation-inducing ligand (APRIL), thereby driving abnormal activation of B cells and the production of pathogenic Gd-IgA1. Similarly, nasal antigens can also activate nasal-associated lymphoid tissue (NALT) through the TLR9 signalling pathway, making it an important source of abnormal glycosylated IgA, ultimately leading to the deposition and damage of renal immune complexes [43].

RA and IgAN share several pathogenic features at the level of the respiratory mucosal immune system, including dysbiosis, breakdown of immune tolerance, and abnormal B cell activation. Both conditions highlight the importance of mucosa-associated lymphoid tissue. However, their core mechanisms differ. RA is primarily driven by the anti-citrullinated protein immune response and NETosis, both of which are initiated within the pulmonary mucosa, while IgAN is characterized by TLR9-driven excessive production of defective IgA. This illustrates the heterogeneity of diseases arising from the same mucosal immune system, influenced by the affected site, the nature of the antigens involved, and the dominant pathogenic pathways.

5. Oral Mucosal Immunity and ADs

Similar to the gut and respiratory tract, the oral cavity contains a complex mucosal immune system, the disruption of which is related to the pathogenesis of ADs.

5.1 Rheumatoid Arthritis

An existing study has found that anti-citrullinated protein antibody (ACPA), anti-carbamylated protein (anti-CARP), and IgA-type anti-aminoacyl protein antibodies (AAPA) can be detected in the saliva of RA patients, suggesting that there may be local secretion of autoantibodies in their oral mucosa [44]. Furthermore, the prevalence of periodontal disease is higher in RA patients compared to healthy individuals, and effective periodontal treatment

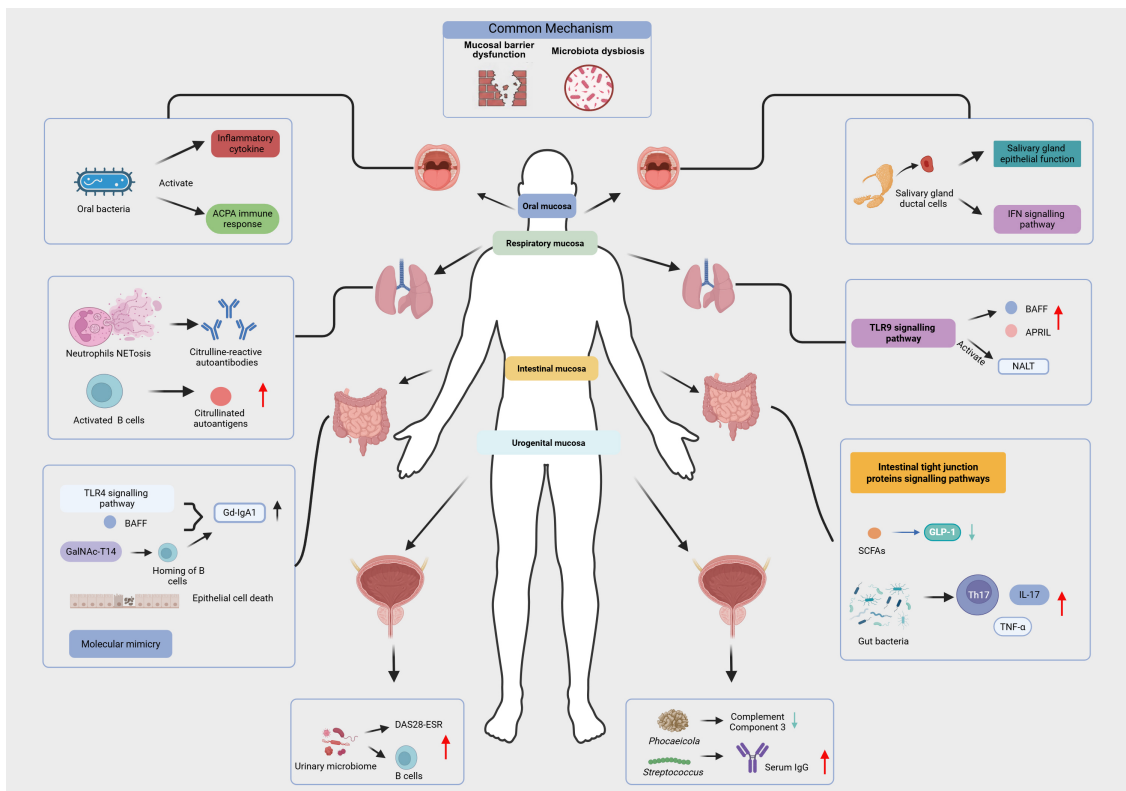


Fig. 2. Mechanisms of cross-mucosal immunity in autoimmune diseases. Notes: ACPA, anti-citrullinated protein antibody; IFN, interferon; TLR, toll-like receptor; GLP-1, glucagon-like peptide-1; Th17, T helper 17; IL-17, interleukin-17; DAS28-ESR, disease activity score in 28 joints-erythrocyte sedimentation rate; IgG, immunoglobulin G; BAFF, B-cell-activating factor; NALT, nasal-associated lymphoid tissue; APRIL, a proliferation-inducing ligand; Gd-IgA1, galactose-deficient immunoglobulin A1; NETosis, neutrophil extracellular trap formation; GalNAc-T14, polypeptide N-acetylgalactosaminyltransferase 14; TNF- α , tumour necrosis factor- α ; SCFAs, short-chain fatty acids. This figure was created using BioRender.com (<https://www.biorender.com/>).

can help improve RA's disease activity [45]. These observations imply that oral mucosal immunity may be associated with RA through mechanisms related to periodontal inflammation. Citrullinated oral bacteria caused by periodontitis repeatedly enter the bloodstream, not only activating the inflammatory monocyte subsets related to synovitis, but also continuously stimulating the ACPA immune response, promoting the spread of autoimmune reactions to endogenous citrullinated antigenic epitopes, thereby aggravating the progression of RA [46]. Notably, Moentadj *et al.* [47] reported that the abundance of *Streptococcus* species is elevated in the oral cavity of patients with RA. Moreover, further research has confirmed that *Streptococcus parasanguinis* strains can induce the production of pro-inflammatory cytokines, such as tumour necrosis factor- α (TNF- α), and that their cell wall components can trigger arthritis in animal models.

5.2 Systemic Lupus Erythematosus

Oral lesions, as common clinical manifestations of SLE, have been included in the diagnostic criteria of the American College of Rheumatology (ACR), among which oral ulcers are one of the important indicators [48]. A meta-

analysis revealed that approximately 31% (95% confidence interval [CI]: 28%, 35%) of SLE patients develop oral mucosal lesions. These lesions manifest in various forms, including typical ulcers, oral erythema, candida infection and purpura [49]. Moreover, the degree of oral microbiota dysbiosis in SLE patients correlates with clinical indicators and disease activity, suggesting that the local oral immune microenvironment is involved in the disease process [50].

5.3 Sjogren's Syndrome

Sjogren's syndrome (SS) mainly affects the salivary glands and lacrimal glands. Chronic inflammation of the glands can cause functional disorders, thereby triggering clinical symptoms mainly characterized by dry mouth and dry eyes [51]. Singh *et al.* [52] reported that levels of *Veillonella parvula* in both subgingival and supragingival plaque samples from SS patients were elevated compared to healthy controls, suggesting that this bacterium may serve as a potential specific microbial biomarker for the disease. Notably, Alam *et al.* [53] further proposed that oral dysbiosis might lead to bacterial invasion into salivary gland ductal cells, thereby interfering with salivary gland epithelial function and activating the type I interferon (IFN) signalling

Table 1. Key mechanisms of mucosal immunity in autoimmune diseases.

Mucosal site	ADs	Mechanisms	References
Intestinal mucosa	SLE	Gut microbiota dysbiosis; Bacterial translocation and molecular mimicry; The elevation of zonulin levels.	[12–14]
Intestinal mucosa	RA	Abnormal activation of intestinal tight junction protein-related signaling pathways; Gut microbiota promotes the expression of IL-17 and Th17-related cytokines and modulate bile acid metabolism.	[16–19]
Intestinal mucosa	IBD	Dysbiosis of the intestinal commensal microbiota; Impairment of intestinal barrier integrity.	[21,22]
Intestinal mucosa	T1DM	Dysbiosis of the gut microbiota impairs SCFA production and subsequently diminishes GLP-1 secretion and drives increased inflammation.	[24–26]
Intestinal mucosa	MS	Microbiota dysbiosis activates MAIT cells, which then enter the central nervous system and produce pro-inflammatory cytokines.	[28–30]
Intestinal mucosa	IgAN	Gut microbiota dysbiosis activates the TLR4 signalling pathway and promotes the expression of BAFF; Abnormal glycosylation of intestinal mucins interferes with the proper homing of B cells to mucosal sites.	[32–34]
Intestinal mucosa	AITD	Microbial dysbiosis drives the secretion of pro-inflammatory factors; Molecular mimicry.	[36,37]
Respiratory mucosa	RA	Abnormal B-cell activation in lung mucosa leading to anti-citrullinated antibodies; Neutrophils in the lungs undergo NETosis, thereby releasing large amounts of citrullinated autoantigens.	[38–40]
Respiratory mucosa	IgAN	Abnormal activation of the TLR9 signaling pathway.	[41–43]
Oral mucosa	RA	Oral bacteria trigger inflammatory cytokine production and drive ACPA immune responses.	[44–47]
Oral mucosa	SLE	Oral mucosal lesions; Oral microbiota dysbiosis correlates with disease indicators.	[49,50]
Oral mucosa	SS	Bacteria invade salivary gland ductal cells, thereby interfering with salivary epithelial function and activating the IFN signalling pathway.	[52,53]
Urogenital mucosa	RA	Urinary microbiota is positively correlated with the DAS28-ESR and peripheral plasma B-cell levels.	[54]
Urogenital mucosa	SLE	Bladder microbiota is associated with C3 and IgG levels.	[55]

Notes: ADs, autoimmune diseases; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; T1DM, type 1 diabetes mellitus; SS, sjogren's syndrome; MS, multiple sclerosis; IgAN, immunoglobulin A nephropathy; AITD, autoimmune thyroid disease; ACPA, anti-citrullinated protein antibody; IFN, interferon; TLR, toll-like receptor; GLP-1, glucagon-like peptide-1; Th17, T helper 17; IL-17, interleukin-17; DAS28-ESR, disease activity score in 28 joints-erythrocyte sedimentation rate; IgG, immunoglobulin G; BAFF, B-cell-activating factor; MAIT, mucosal-associated invariant T; C3, component 3; SCFA, short-chain fatty acid.

pathway. Furthermore, bacterial infection of the salivary glands may persistently exacerbate local inflammation and secretory dysfunction, ultimately driving the pathological progression of SS.

Overall, these findings suggest that although dysbiosis and barrier dysfunction in the oral cavity are common features of RA, SLE, and SS, the downstream pathogenic pathways differ significantly. RA is primarily driven by oral pathogen-induced molecular mimicry and the systemic dissemination of autoantibodies. SLE is characterised by a correlation between typical mucosal ulcerations and disease activity, whereas SS involves direct bacterial invasion into ductal cells and the subsequent activation of the IFN signalling pathway, ultimately leading to glandular dysfunction. This difference highlights that while restoring oral microbial homeostasis is a universal therapeutic goal, it is essential to address the unique mucosal immunopathology of each disease.

6. Urogenital Mucosal Immunity and ADs

Beyond the gut, respiratory tract, and oral mucosa, urogenital tract stands as another critical immune interface. Dysbiosis in its microbiota and associated local immune dysregulation have also been demonstrated to correlate with certain ADs. In RA patients, the urinary microbiome exhibits characteristic alterations, marked by a significant increase in the relative abundance of *Proteus*, *Enterococcus*, and *Bacteroides*. Notably, the enrichment of these genera correlates positively with the disease activity score in 28 joints-erythrocyte sedimentation rate (DAS28-ESR) and peripheral plasma B-cell levels [54]. Similarly, in the bladder microbiota of patients with SLE, comparable associations between microbial composition and immune markers have been observed. Specifically, the abundance of *Megasphaera* and *Phocaeicola* correlates negatively with serum complement component 3 (C3) levels, whereas *Streptococcus* shows a positive correlation with serum immunoglob-

ulin G (IgG) levels [55]. These findings suggest that the urogenital mucosa may modulate local and systemic immune responses through its specific microbial composition, thereby influencing the pathological progression of ADs.

The above findings have indicated that mucosal immune disorders are involved in the occurrence and development of ADs. Although the mucosal sites and specific immune mechanisms involved in different diseases have their own focuses, there are also important common pathways and interrelationships among them. The key mechanisms of mucosal immunity in ADs are shown in Table 1 (Ref. [12–14,16–19,21,22,24–26,28–30,32–34,36–47,49,50,52–55]). Furthermore, we have provided an integrative diagram of cross-mucosal mechanisms in ADs (Fig. 2).

7. New Prospective Therapy Targeting the Mucosal Immunity

In the clinical management of ADs, systemic immunosuppressive therapy remains the basic approach. However, more targeted mucosal intervention strategies are increasingly attracting attention and becoming important supplementary means and cutting-edge directions. These therapies aim to restore immune tolerance, repair mucosal barriers or precisely regulate specific immune pathways.

7.1 Restoring the Barrier or Microbiome Homeostasis

7.1.1 Probiotics

Probiotics, an adjunct therapy, have garnered increasing attention for their potential to promote health. They have also demonstrated promising applications in the treatment of ADs, exerting positive effects by modulating intestinal immune balance and systemic inflammatory responses [54–61] (Table 2, Ref. [56–75]). Nevertheless, several clinical trials indicate that probiotics may be ineffective or even lead to adverse effects in certain conditions. For instance, a randomized controlled trial revealed that *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb12 strains did not significantly maintain residual pancreatic β -cell function in newly diagnosed children with T1DM [76]. A Japanese study involving patients with quiescent UC was terminated early because *Bifidobacterium breve* strain Yakult therapy did not show superior efficacy compared to placebo in delaying recurrence [77]. Additionally, it has been indicated that MS patients undergoing probiotic treatment may experience adverse events, including diarrhea, abdominal pain, constipation, weight gain, nausea, and exacerbation of fatigue [78]. While probiotics exhibit a certain regulatory potential in the treatment of ADs, their benefits are not universal. Depending on the type of disease, and individual variations, administering probiotics can result in outcomes ranging from effective to ineffective or even harmful. Therefore, the use of probiotics in clinical practice and health management should be guided by a comprehensive assessment of the specific disease context, the

available clinical evidence, the characteristics of the probiotic strains used, and individual patient factors. A cautious and personalized approach is warranted, avoiding the misconception that probiotics constitute a universal treatment method.

7.1.2 Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) aims to restore gut microbiota balance and improve clinical outcomes by transferring the fecal microbiota from healthy donors to recipients [79]. This therapy, through the pivotal process of resetting the gut microbiome, has shown potential to alleviate symptoms across various ADs. Existing evidence spans from animal studies to clinical observations, supporting its value as an emerging therapeutic strategy, with specific positive effects (Table 2). Nonetheless, in practical applications, FMT still faces numerous unresolved issues and risks. Common adverse reactions include gastrointestinal symptoms such as bloating, diarrhea, and constipation [80]. The associated risks are particularly significant for immunocompromised individuals, as FMT may lead to severe adverse events like bacteremia, sepsis, and even multiple organ failure [81]. Notably, the effectiveness of FMT in ADs is not always positive. For instance, in a RA mouse model, FMT did not demonstrate a significant improvement in arthritis symptoms [82]. Additionally, germ-free mice that received fecal microbiota from donors with RA or IBD exhibited pathological changes such as cartilage alterations, claw deformities, elevated inflammatory mediators, and T lymphocyte activation, alongside behavioral abnormalities, occult bleeding, and gut dysfunction [83]. These findings suggest that the therapeutic outcome of FMT is not guaranteed and can be paradoxically detrimental, depending critically on the disease-specific composition and functional state of the donor microbiota.

7.1.3 Diet

Dietary patterns play a complex and crucial role in the management of ADs. In T1DM, the Mediterranean diet may help delay disease progression and reduce the risk of cardiovascular complications by modulating gut microbiota composition, preserving intestinal barrier integrity, and thereby regulating host immune responses [71]. Similarly, a high-fiber diet rich in pectin and inulin can alleviate arthritis symptoms in CIA mice by modulating the gut microbiota and regulating the abundance of butyrate [72]. This suggests that a high-fiber diet may have the potential to modulate the immune-inflammatory response in RA. In the case of SLE, dietary fiber interventions that adjust the composition of the gut microbiota can rebalance the dysfunction of the gut-immune system-vascular wall axis, thereby preventing the onset of hypertension [73]. Insoluble dietary fibers combined with polyphenols improve outcomes in dextran sulfate sodium (DSS)-induced UC in mice by increasing beneficial bacteria and reducing harmful bacteria

Table 2. Novel therapeutic approaches targeting intestinal mucosal immunity and ADs.

Representative method	Primary effect	ADs	References
Probiotics	Increase levels of IL-2, FOXP3, IL-10, and TGF- β , while reducing levels of IL-6.	SLE	[56]
Probiotics	Suppresses serum inflammatory cytokines in rats with CIA; Reduce joint swelling and cartilage tissue damage in rats with AIA.	RA	[57,58]
Probiotic Capsules	Improve fasting and postprandial blood glucose and lipid levels.	T1DM	[59]
Probiotics	Improve hemoglobin, hematocrit, CRP, IgA, and IL-10 levels in UC patients.	UC	[60]
Probiotics	Increase BDNF levels in MS patients and reduce IL-6 level.	MS	[61]
Probiotics	Reduce IgA complex deposition and mesangial proliferation.	IgAN	[62]
FMT	Correct abnormal hypomethylation; Reduce SLEDAI-2K scores and the level of serum anti-dsDNA antibody.	SLE	[63]
FMT	Lower the DAS28 score.	RA	[64]
FMT	Control blood sugar levels and improve insulin resistance.	T1DM	[65]
FMT	Restore the patient's gut microbiota to alleviate the disease.	IBD	[66]
FMT	Alleviate neurological symptoms in MS patients; Enhance neural function, reduce IL-17 levels, and restore intestinal homeostasis.	MS	[67,68]
FMT	Reduce urinary protein levels in patients.	IgAN	[69]
FMT	Elevate levels of free thyroxine and free triiodothyronine.	AITD	[70]
Mediterranean diet	Modulate the composition of the gut microbiota and maintain the integrity of the gut barrier.	T1DM	[71]
Diet rich in pectin and inulin	Modulate the immune-inflammatory response.	RA	[72]
High-fiber diet	Rebalance the dysfunction of the gut-immune system-vascular wall axis.	SLE	[73]
Insoluble dietary fibers combined with polyphenols	Increase beneficial bacteria counts and reduce harmful bacteria abundance to improve disease prognosis.	UC	[74]
Gluten-free diet	Reduce the deposition of immune complexes.	IgAN	[75]

Notes: ADs, autoimmune diseases; FOXP3, forkhead box protein 3; TGF- β , transforming growth factor β ; CIA, collagen-induced arthritis; AIA, Adjuvant-Induced Arthritis; CRP, C-reactive protein; IL-2, interleukin-2; IL-10, interleukin-10; IL-6, interleukin-6; UC, ulcerative colitis; BDNF, Brain-Derived Neurotrophic Factor; FMT, fecal microbiota transplantation; SLEDAI-2K, systemic lupus erythematosus disease activity index 2000; DAS28, disease activity score in 28 joints; AITD, autoimmune thyroid disease; IgA, immunoglobulin A.

abundance [74]. However, not all high-fiber diets are universally beneficial. Unfermented β -glucan fibers may exacerbate inflammatory responses in some patients with IBD by promoting the secretion of pro-inflammatory cytokines [84]. These findings suggest that specific dietary fibers can have adverse effects, highlighting the need for personalized dietary fiber interventions tailored to different diseases. A study has indicated that a gluten-free diet may reduce the deposition of immune complexes and the severity of the disease in patients with IgAN [75]. However, research has suggested that a gluten-free diet may negatively impact the gut microbiota in women with AITD, thereby exacerbating the inflammatory response [85]. This further emphasizes the importance of individualized dietary adjustments based on the specific characteristics of each disease.

7.2 Local Immune Modulation

7.2.1 Mucosal Delivery

Mucosal administration through nasal, oral, sublingual and rectal routes are non-invasive systemic approach to drug delivery. It offers several advantages, including ease

of self-administration, rapid onset of action, and reduced first-pass metabolism, thereby facilitating prompt symptom control [86]. Additionally, this approach may induce more potent immune responses than traditional administration routes. By activating the shared mucosal immune system, this strategy can simultaneously trigger both effective systemic and localized mucosal immune responses, an outcome that is difficult to achieve with systemic delivery methods such as intravenous injection. Effective mucosal immune induction can also prevent pathogens from invading the body via mucosal pathways [87]. This strategy has demonstrated potential in both clinical trials and animal studies of ADs. In the experimental autoimmune encephalomyelitis (EAE) mice models, nasal administration enables the drug to pass the blood-brain barrier through the naso-brain pathway, allowing direct delivery to the central nervous system, thereby enhancing the therapeutic effect [88]. Clinically, targeted-release formulations like budesonide (Nefecon) are used to treat IgAN. These formulations are designed for precise delivery to the Peyer's patches in the ileum, thereby inhibiting the local immune

response while minimizing systemic adverse effects [89]. Notably, for the treatment of UC, the chitosan-modified microemulsion encapsulated nobiletin (NOB-CS-ME) can penetrate deep into the intestinal mucus layer, overcoming the limitations imposed by the intestinal mucus barrier. This approach enhances targeted delivery to the colonic epithelium, promoting the reconstruction of the intestinal barrier function and balancing M1/M2 polarization of macrophages, while inhibiting local inflammatory cascades [90].

7.2.2 Vaccines

Mucosal vaccines are immunological agents delivered through mucosal surfaces such as the respiratory and gastrointestinal tracts, while nanoparticle vaccines utilize advanced delivery systems based on nano-sized carriers to transport antigens or immunomodulatory molecules. These nanoparticle vaccines demonstrate enhanced targeting efficiency for the mucosal immune system and hold promise for overcoming the limitations of traditional mucosal vaccines [91]. Some studies indicate that nanoparticle vaccines exhibit unique advantages in the treatment of ADs. By targeting antigen-presenting cells in mucosal-associated lymphoid tissues, they can induce antigen-specific immune tolerance rather than activation. Specifically, poly (lactide-co-glycolide) (PLG) nanoparticles loaded with protein lipid peptide delivered to the lungs can effectively intercept autoreactive T cells migrating to the central nervous system, alleviating symptoms in animal models of MS [92]. Similarly, oral administration of targeting nanoparticles loaded with heat shock protein 65-6×P277 (H6P) can deliver H6P to DCs in the gut of non-obese diabetic (NOD) mice, thereby inducing antigen-specific T-cell tolerance and preventing the onset of autoimmune diabetes [93]. In contrast to traditional broad-spectrum immunosuppressants, this vaccine strategy aims to precisely reprogram aberrant immune responses while maintaining the overall immune defense function of the body. This approach offers a new therapeutic paradigm for ADs such as MS and T1DM, characterized by its targeting, durability, and safety, and represents a forefront development direction in precision immune interventions. It should be noted that research on inducing immune tolerance via mucosal nano-vaccine through mucosal immune pathways is still in its early stages, and the underlying mechanisms of immune regulation require further in-depth study.

7.3 Precision Targeting

7.3.1 Biologics

With the continuous emergence and clinical application of various novel monoclonal antibodies, the arsenal of precision targeted therapies for IBD continues to expand. As first-line treatments for IBD, these agents effectively alleviate intestinal inflammation and promote mucosal healing [94]. In the treatment of MS, interferon- β (IFN- β),

as a classic disease-modifying therapy, has been found to modulate the composition of the gut microbiota in addition to its direct immunoregulatory effects [95]. MS patients undergoing IFN- β treatment exhibit altered gut microbiota metabolites, characterized by a significant elevation in serum propionate levels. As a kind of SCFA, propionate promotes the induction and activity of Tregs, an immunomodulatory mechanism associated with the amelioration of MS disease progression. These findings underscore the value of biologics in the treatment of ADs. Beyond directly targeting key inflammatory pathways, these agents may exert synergistic therapeutic effects by modulating the immune microenvironment and influencing microbiota metabolism, thereby continually driving the management of ADs toward a more precise and comprehensive future.

7.3.2 Small-Molecule Drugs

Small molecular drugs are expanding the boundaries of ADs treatment through multiple mechanisms. In the field of MS, the dimethyl fumarate (DMF) not only directly modulates immune cell function but also reshapes gut microbiota by reducing the abundance of *Lachnospiraceae* and *Veillonellaceae*, while regulating vitamin A metabolic pathways, thereby forming an intestinal-brain axis immune regulation network [96]. In the treatment of CD, the novel drug Upadacitinib has shown potential in promoting intestinal mucus healing and achieving endoscopic remission [97]. These advancements highlight the promising application of small molecule drugs in the treatment of ADs by synergistically regulating the immune system and gut microenvironment, while directly promoting mucosal repair.

8. Conclusion

This review summarizes that the dysregulation of mucosal immunity, characterized by barrier dysfunction and dysbiosis plays a crucial role in the pathogenesis of ADs. Therapeutic strategies targeting mucosal immunity are therefore expanding the current treatment landscape for ADs. Nonetheless, significant challenges remain, mainly due to the inter-individual heterogeneity in mucosal immune responses and insufficient understanding of mucosal immunopathological mechanisms in ADs. Future research should prioritise several key directions. First, integrating multi-omics technologies to reveal the underlying mechanisms linking mucosal immunity and ADs. Secondly, developing personalized intervention strategies based on individual microbiomes, such as utilizing next-generation probiotics or metabolic products to target specific immune-metabolic pathways. Finally, constructing novel mucosal vaccine carriers and delivery systems to achieve precise localization and controlled release of antigens or drugs at mucosal sites. These advances have the potential to drive a paradigm shift in ADs treatment, moving it from traditional systemic immunosuppression to the precise modulation of

mucosal immunity. Such a shift represents a key step towards disease modification and lays an important foundation for establishing long-term and stable disease management pathways.

Key Points

- Mucosal immune dysregulation is an early and specific driving factor of autoimmune diseases, potentially occurring before the clinical manifestations of the disease appear.
- Although mucosal barrier impairment and microbial imbalance form a common pathological basis, different mucosal regions still shape disease-specific immune pathways, with disease phenotypes determined by region-specific and pathway-specific mechanisms.
- Emerging strategies targeting mucosal immunity through targeted mucosal delivery, nano-vaccines, microbiome interventions, and precision biologicals enable a shift from broad immunosuppression to precise, disease-modifying therapies.

Availability of Data and Materials

Not applicable.

Author Contributions

HFW, HAM, SST, and HFP made substantial contributions to the conception and design of the review. HFW and HAM jointly conceived the study and drafted the initial manuscript. All authors made substantial contributions to conception. All authors contributed to revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This study was funded by grants from the National Natural Science Foundation of China (82504495, 82273710).

Conflict of Interest

Hai-Feng Pan is serving as one of the Editorial Board Members of this journal. We declare that Hai-Feng Pan had no involvement in the review of this article and has no access to information regarding its review. The authors declare no conflict of interest. Full responsibility for the editorial process for this article was delegated to Arianna Di Stadio.

References

- [1] Pisetsky DS. Pathogenesis of autoimmune disease. *Nature Reviews. Nephrology*. 2023; 19: 509–524. <https://doi.org/10.1038/s41581-023-00720-1>.
- [2] Wiedermann U. Mucosal immunity–mucosal tolerance. A strategy for treatment of allergic diseases. *Chemical Immunology and Allergy*. 2003; 82: 11–24. <https://doi.org/10.1159/000071551>.
- [3] Ptasiwicz M, Grywalska E, Mertowska P, Korona-Główniak I, Poniewierska-Baran A, Niedźwiedzka-Rystwej P, *et al.* Armed to the Teeth-The Oral Mucosa Immunity System and Microbiota. *International Journal of Molecular Sciences*. 2022; 23: 882. <https://doi.org/10.3390/ijms23020882>.
- [4] Zhou X, Wu Y, Zhu Z, Lu C, Zhang C, Zeng L, *et al.* Mucosal immune response in biology, disease prevention and treatment. *Signal Transduction and Targeted Therapy*. 2025; 10: 7. <https://doi.org/10.1038/s41392-024-02043-4>.
- [5] Zhang Z, Hong W, Zhang Y, Li X, Que H, Wei X. Mucosal immunity and vaccination strategies: current insights and future perspectives. *Molecular Biomedicine*. 2025; 6: 57. <https://doi.org/10.1186/s43556-025-00301-7>.
- [6] Mettelman RC, Allen EK, Thomas PG. Mucosal immune responses to infection and vaccination in the respiratory tract. *Immunity*. 2022; 55: 749–780. <https://doi.org/10.1016/j.immuni.2022.04.013>.
- [7] Wang J, He M, Yang M, Ai X. Gut microbiota as a key regulator of intestinal mucosal immunity. *Life Sciences*. 2024; 345: 122612. <https://doi.org/10.1016/j.lfs.2024.122612>.
- [8] Tsai CJY, Loh JMS, Fujihashi K, Kiyono H. Mucosal vaccination: onward and upward. *Expert Review of Vaccines*. 2023; 22: 885–899. <https://doi.org/10.1080/14760584.2023.2268724>.
- [9] An J, Liu Y, Wang Y, Fan R, Hu X, Zhang F, *et al.* The Role of Intestinal Mucosal Barrier in Autoimmune Disease: A Potential Target. *Frontiers in Immunology*. 2022; 13: 871713. <https://doi.org/10.3389/fimmu.2022.871713>.
- [10] Allaire JM, Crowley SM, Law HT, Chang SY, Ko HJ, Vallance BA. The Intestinal Epithelium: Central Coordinator of Mucosal Immunity. *Trends in Immunology*. 2018; 39: 677–696. <https://doi.org/10.1016/j.it.2018.04.002>.
- [11] Siegel CH, Sammaritano LR. Systemic Lupus Erythematosus: A Review. *JAMA*. 2024; 331: 1480–1491. <https://doi.org/10.1001/jama.2024.2315>.
- [12] Pan Q, Guo F, Huang Y, Li A, Chen S, Chen J, *et al.* Gut Microbiota Dysbiosis in Systemic Lupus Erythematosus: Novel Insights into Mechanisms and Promising Therapeutic Strategies. *Frontiers in Immunology*. 2021; 12: 799788. <https://doi.org/10.3389/fimmu.2021.799788>.
- [13] Katsushima M, Nakayama Y, Yoshida T, Nishida Y, Shirakashi M, Nakashima R, *et al.* Association of gut commensal translocation with autoantibody production in systemic lupus erythematosus. *Rheumatology*. 2025; 64: 3104–3115. <https://doi.org/10.1093/rheumatology/keae476>.
- [14] Bowes MM, Casares-Marfil D, Sawalha AH. Intestinal permeability correlates with disease activity and DNA methylation changes in lupus patients. *Clinical Immunology*. 2024; 262: 110173. <https://doi.org/10.1016/j.clim.2024.110173>.
- [15] Gravallesse EM, Firestein GS. Rheumatoid Arthritis - Common Origins, Divergent Mechanisms. *The New England Journal of Medicine*. 2023; 388: 529–542. <https://doi.org/10.1056/NEJMr2103726>.
- [16] Jubair WK, Hendrickson JD, Severs EL, Schulz HM, Adhikari S, Ir D, *et al.* Modulation of Inflammatory Arthritis in Mice by Gut Microbiota Through Mucosal Inflammation and Autoantibody Generation. *Arthritis & Rheumatology*. 2018; 70: 1220–1233. <https://doi.org/10.1002/art.40490>.

- [17] Tajik N, Frech M, Schulz O, Schäler F, Lucas S, Azizov V, *et al.* Targeting zonulin and intestinal epithelial barrier function to prevent onset of arthritis. *Nature Communications*. 2020; 11: 1995. <https://doi.org/10.1038/s41467-020-15831-7>.
- [18] Nii T, Maeda Y, Motooka D, Naito M, Matsumoto Y, Ogawa T, *et al.* Genomic repertoires linked with pathogenic potency of arthritogenic *Prevotella copri* isolated from the gut of patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases*. 2023; 82: 621–629. <https://doi.org/10.1136/ard-2022-222881>.
- [19] Sun H, Guo Y, Wang H, Yin A, Hu J, Yuan T, *et al.* Gut commensal *Parabacteroides distasonis* alleviates inflammatory arthritis. *Gut*. 2023; 72: 1664–1677. <https://doi.org/10.1136/gutjnl-2022-327756>.
- [20] Bisgaard TH, Allin KH, Keefer L, Ananthakrishnan AN, Jess T. Depression and anxiety in inflammatory bowel disease: epidemiology, mechanisms and treatment. *Nature Reviews. Gastroenterology & Hepatology*. 2022; 19: 717–726. <https://doi.org/10.1038/s41575-022-00634-6>.
- [21] Alexandrescu L, Nicoara AD, Tofolean DE, Herlo A, Nelson Twakor A, Tocia C, *et al.* Healing from Within: How Gut Microbiota Predicts IBD Treatment Success-A Systematic Review. *International Journal of Molecular Sciences*. 2024; 25: 8451. <https://doi.org/10.3390/ijms25158451>.
- [22] Kong C, Yang M, Yue N, Zhang Y, Tian C, Wei D, *et al.* Restore Intestinal Barrier Integrity: An Approach for Inflammatory Bowel Disease Therapy. *Journal of Inflammation Research*. 2024; 17: 5389–5413. <https://doi.org/10.2147/JIR.S470520>.
- [23] Herold KC, Krischer JP. The Pathogenesis of Type 1 Diabetes. *Cold Spring Harbor Perspectives in Medicine*. 2025; 15: a041623. <https://doi.org/10.1101/cshperspect.a041623>.
- [24] Haque S, Bima AI, Babalghith AO, Jalal NA, Aldairi AF, Wahid M, *et al.* Distinct gut microbiota signatures and metabolic dysregulation in individuals with type 1 diabetes: insights into a microbiome-metabolite axis. *Gut Pathogens*. 2025; 17: 98. <https://doi.org/10.1186/s13099-025-00779-0>.
- [25] Vatanen T, de Beaufort C, Marcovecchio ML, Overbergh L, Brunak S, Peakman M, *et al.* Gut microbiome shifts in people with type 1 diabetes are associated with glycaemic control: an INNODIA study. *Diabetologia*. 2024; 67: 1930–1942. <https://doi.org/10.1007/s00125-024-06192-7>.
- [26] Huang S, Li F, Quan C, Jin D. Intestinal flora: a potential pathogenesis mechanism and treatment strategy for type 1 diabetes mellitus. *Gut Microbes*. 2024; 16: 2423024. <https://doi.org/10.1080/19490976.2024.2423024>.
- [27] McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and Treatment of Multiple Sclerosis: A Review. *JAMA*. 2021; 325: 765–779. <https://doi.org/10.1001/jama.2020.26858>.
- [28] Ordoñez-Rodríguez A, Roman P, Rueda-Ruzafa L, Campos-Rios A, Cardona D. Changes in Gut Microbiota and Multiple Sclerosis: A Systematic Review. *International Journal of Environmental Research and Public Health*. 2023; 20: 4624. <https://doi.org/10.3390/ijerph20054624>.
- [29] Gargano F, Guerrero G, Piras E, Serafini B, Di Paola M, Rizzetto L, *et al.* Proinflammatory mucosal-associated invariant CD8+ T cells react to gut flora yeasts and infiltrate multiple sclerosis brain. *Frontiers in Immunology*. 2022; 13: 890298. <https://doi.org/10.3389/fimmu.2022.890298>.
- [30] Zibler J, Rothhammer V, Linnerbauer M. Gut-Brain Interactions and Their Impact on Astrocytes in the Context of Multiple Sclerosis and Beyond. *Cells*. 2024; 13: 497. <https://doi.org/10.3390/cells13060497>.
- [31] Del Vecchio L, Allinovi M, Comolli S, Peiti S, Rimoldi C, Locatelli F. Drugs in Development to Treat IgA Nephropathy. *Drugs*. 2024; 84: 503–525. <https://doi.org/10.1007/s40265-024-02036-1>.
- [32] Hu X, Du J, Xie Y, Huang Q, Xiao Y, Chen J, *et al.* Fecal microbiota characteristics of Chinese patients with primary IgA nephropathy: a cross-sectional study. *BMC Nephrology*. 2020; 21: 97. <https://doi.org/10.1186/s12882-020-01741-9>.
- [33] Zhu Y, He H, Sun W, Wu J, Xiao Y, Peng Y, *et al.* IgA nephropathy: gut microbiome regulates the production of hypoglycosylated IgA1 via the TLR4 signaling pathway. *Nephrology, Dialysis, Transplantation*. 2024; 39: 1624–1641. <https://doi.org/10.1093/ndt/gfae052>.
- [34] Gleeson PJ, Cogné M, Monteiro RC. Mucin O-glycosylation and B-cell homing: a new bridge for the gut-kidney axis in IgA nephropathy? *Kidney International*. 2026; 109: 258–261. <https://doi.org/10.1016/j.kint.2025.08.040>.
- [35] Martínez-Hernández R, Sánchez de la Blanca N, Sacristán-Gómez P, Serrano-Somavilla A, Muñoz De Nova JL, Sánchez Cabo F, *et al.* Unraveling the molecular architecture of autoimmune thyroid diseases at spatial resolution. *Nature Communications*. 2024; 15: 5895. <https://doi.org/10.1038/s41467-024-50192-5>.
- [36] Sessa L, Malavolta E, Sodero G, Cipolla C, Rigante D. The conspiring role of gut microbiota as primer of autoimmune thyroid diseases: A scoping focus. *Autoimmunity Reviews*. 2025; 24: 103780. <https://doi.org/10.1016/j.autrev.2025.103780>.
- [37] Virili C, Stramazzo I, Centanni M. Gut microbiome and thyroid autoimmunity. *Best Practice & Research. Clinical Endocrinology & Metabolism*. 2021; 35: 101506. <https://doi.org/10.1016/j.beem.2021.101506>.
- [38] Joshua V, Loberg Haarhaus M, Hensvold A, Wähämaa H, Gerstner C, Hansson M, *et al.* Rheumatoid Arthritis-Specific Autoimmunity in the Lung Before and at the Onset of Disease. *Arthritis & Rheumatology*. 2023; 75: 1910–1922. <https://doi.org/10.1002/art.42549>.
- [39] Joo YB, Lee J, Park YJ, Bang SY, Kim K, Lee HS. Associations of upper respiratory mucosa microbiota with Rheumatoid arthritis, autoantibodies, and disease activity. *PLoS ONE*. 2024; 19: e0308010. <https://doi.org/10.1371/journal.pone.0308010>.
- [40] Okamoto Y, Devoe S, Seto N, Minarchick V, Wilson T, Rothfuss HM, *et al.* Association of Sputum Neutrophil Extracellular Trap Subsets With IgA Anti-Citrullinated Protein Antibodies in Subjects at Risk for Rheumatoid Arthritis. *Arthritis & Rheumatology*. 2022; 74: 38–48. <https://doi.org/10.1002/art.41948>.
- [41] Yuan X, Qing J, Zhi W, Wu F, Yan Y, Li Y. Gut and respiratory microbiota landscapes in IgA nephropathy: a cross-sectional study. *Renal Failure*. 2024; 46: 2399749. <https://doi.org/10.1080/0886022X.2024.2399749>.
- [42] Kano T, Suzuki H, Makita Y, Nihei Y, Fukao Y, Nakayama M, *et al.* Mucosal Immune System Dysregulation in the Pathogenesis of IgA Nephropathy. *Biomedicines*. 2022; 10: 3027. <https://doi.org/10.3390/biomedicines10123027>.
- [43] Kano T, Suzuki H, Makita Y, Fukao Y, Suzuki Y. Nasal-associated lymphoid tissue is the major induction site for nephritogenic IgA in murine IgA nephropathy. *Kidney International*. 2021; 100: 364–376. <https://doi.org/10.1016/j.kint.2021.04.026>.
- [44] Derksen VFAM, Martinsson K, van Mourik AG, Wagenaar CA, Toes REM, Walrabenstein W, *et al.* Evidence of Site-Specific Mucosal Autoantibody Secretion in Rheumatoid Arthritis. *Arthritis & Rheumatology*. 2025; 77: 272–282. <https://doi.org/10.1002/art.43036>.
- [45] Moura MF, Cota LOM, Silva TA, Cortelli SC, Ferreira GA, López MM, *et al.* Clinical and microbiological effects of non-surgical periodontal treatment in individuals with rheumatoid arthritis: a controlled clinical trial. *Odontology*. 2021; 109: 484–493. <https://doi.org/10.1007/s10266-020-00566-0>.
- [46] Brewer RC, Lanz TV, Hale CR, Sepich-Poore GD, Martino C, Swafford AD, *et al.* Oral mucosal breaks trigger anti-citrullinated bacterial and human protein antibody responses in

- rheumatoid arthritis. *Science Translational Medicine*. 2023; 15: eabq8476. <https://doi.org/10.1126/scitranslmed.abq8476>.
- [47] Moentadj R, Wang Y, Bowerman K, Rehaume L, Nel H, O Cuiv P, *et al.* *Streptococcus* species enriched in the oral cavity of patients with RA are a source of peptidoglycan-polysaccharide polymers that can induce arthritis in mice. *Annals of the Rheumatic Diseases*. 2021; 80: 573–581. <https://doi.org/10.1136/annrheumdis-2020-219009>.
- [48] Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis and Rheumatism*. 1982; 25: 1271–1277. <https://doi.org/10.1002/art.1780251101>.
- [49] Du F, Qian W, Zhang X, Zhang L, Shang J. Prevalence of oral mucosal lesions in patients with systemic Lupus Erythematosus: a systematic review and meta-analysis. *BMC Oral Health*. 2023; 23: 1030. <https://doi.org/10.1186/s12903-023-03783-5>.
- [50] Guo J, Cui G, Huang W, Zheng Z, Li T, Gao G, *et al.* Alterations in the human oral microbiota in systemic lupus erythematosus. *Journal of Translational Medicine*. 2023; 21: 95. <https://doi.org/10.1186/s12967-023-03892-3>.
- [51] Baldini C, Fulvio G, La Rocca G, Ferro F. Update on the pathophysiology and treatment of primary Sjögren syndrome. *Nature Reviews. Rheumatology*. 2024; 20: 473–491. <https://doi.org/10.1038/s41584-024-01135-3>.
- [52] Singh M, Teles F, Uzel NG, Papas A. Characterizing Microbiota from Sjögren's Syndrome Patients. *JDR Clinical and Translational Research*. 2021; 6: 324–332. <https://doi.org/10.1177/2380084420940623>.
- [53] Alam J, Lee A, Lee J, Kwon DI, Park HK, Park JH, *et al.* Dysbiotic oral microbiota and infected salivary glands in Sjögren's syndrome. *PLoS ONE*. 2020; 15: e0230667. <https://doi.org/10.1371/journal.pone.0230667>.
- [54] Jin J, Li J, Hou M, Ding X, Zhong Y, He J, *et al.* A Shifted Urinary Microbiota Associated with Disease Activity and Immune Responses in Rheumatoid Arthritis. *Microbiology Spectrum*. 2023; 11: e0366222. <https://doi.org/10.1128/spectrum.03662-22>.
- [55] Liu F, Du J, Zhai Q, Hu J, Miller AW, Ren T, *et al.* The Bladder Microbiome, Metabolome, Cytokines, and Phenotypes in Patients with Systemic Lupus Erythematosus. *Microbiology Spectrum*. 2022; 10: e0021222. <https://doi.org/10.1128/spectrum.00212-22>.
- [56] Alaei A, Mahmoudi M, Sahebari M, Vahidi Z, Tabasi N, Rastin M. The effects of *Lactobacillus delbrueckii* and *Lactobacillus rhamnosus* on cytokines and their related molecules: An *ex vivo* study on patients with systemic lupus erythematosus. *Archives of Rheumatology*. 2023; 38: 642–652. <https://doi.org/10.46497/ArchRheumatol.2023.9941>.
- [57] Fan Z, Yang B, Ross RP, Stanton C, Shi G, Zhao J, *et al.* Protective effects of *Bifidobacterium adolescentis* on collagen-induced arthritis in rats depend on timing of administration. *Food & Function*. 2020; 11: 4499–4511. <https://doi.org/10.1039/d0fo00077a>.
- [58] Pan H, Guo R, Ju Y, Wang Q, Zhu J, Xie Y, *et al.* A single bacterium restores the microbiome dysbiosis to protect bones from destruction in a rat model of rheumatoid arthritis. *Microbiome*. 2019; 7: 107. <https://doi.org/10.1186/s40168-019-0719-1>.
- [59] Zhang X, Zhang Y, Luo L, Le Y, Li Y, Yuan F, *et al.* The Beneficial Effects of a Multispecies Probiotic Supplement on Glycaemic Control and Metabolic Profile in Adults with Type 1 Diabetes: A Randomised, Double-Blinded, Placebo-Controlled Pilot-Study. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*. 2023; 16: 829–840. <https://doi.org/10.2147/DMSO.S400119>.
- [60] Agraib LM, Yamani MI, Tayyem R, Abu-Sneineh AT, Rayyan YM. Probiotic supplementation induces remission and changes in the immunoglobulins and inflammatory response in active ulcerative colitis patients: A pilot, randomized, double-blind, placebo-controlled study. *Clinical Nutrition ESPEN*. 2022; 51: 83–91. <https://doi.org/10.1016/j.clnesp.2022.08.020>.
- [61] Rahimlou M, Hosseini SA, Majdinasab N, Haghhighizadeh MH, Husain D. Effects of long-term administration of Multi-Strain Probiotic on circulating levels of BDNF, NGF, IL-6 and mental health in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled trial. *Nutritional Neuroscience*. 2022; 25: 411–422. <https://doi.org/10.1080/1028415X.2020.1758887>.
- [62] Tan J, Dong L, Jiang Z, Tan L, Luo X, Pei G, *et al.* Probiotics ameliorate IgA nephropathy by improving gut dysbiosis and blunting NLRP3 signaling. *Journal of Translational Medicine*. 2022; 20: 382. <https://doi.org/10.1186/s12967-022-03585-3>.
- [63] Huang C, Yi P, Zhu M, Zhou W, Zhang B, Yi X, *et al.* Safety and efficacy of fecal microbiota transplantation for treatment of systemic lupus erythematosus: An EXPLORER trial. *Journal of Autoimmunity*. 2022; 130: 102844. <https://doi.org/10.1016/j.jaut.2022.102844>.
- [64] Zeng J, Peng L, Zheng W, Huang F, Zhang N, Wu D, *et al.* Fecal microbiota transplantation for rheumatoid arthritis: A case report. *Clinical Case Reports*. 2020; 9: 906–909. <https://doi.org/10.1002/ccr3.3677>.
- [65] He L, Chen R, Zhang B, Zhang S, Khan BA, Zhu D, *et al.* Fecal microbiota transplantation treatment of autoimmune-mediated type 1 diabetes mellitus. *Frontiers in Immunology*. 2022; 13: 930872. <https://doi.org/10.3389/fimmu.2022.930872>.
- [66] Lahoud C, Habib T, Kalta D, Dimachkie R, El Sayegh S, Deeb L. Intestinal Microbiota and Fecal Transplantation in Patients with Inflammatory Bowel Disease and *Clostridioides difficile*: An Updated Literature Review. *Journal of Clinical Medicine*. 2025; 14: 5260. <https://doi.org/10.3390/jcm14155260>.
- [67] Laeeq T, Vongsavath T, Tun KM, Hong AS. The Potential Role of Fecal Microbiota Transplant in the Reversal or Stabilization of Multiple Sclerosis Symptoms: A Literature Review on Efficacy and Safety. *Microorganisms*. 2023; 11: 2840. <https://doi.org/10.3390/microorganisms11122840>.
- [68] Xu D, Ren L, Zhang W, Wu S, Yu M, He X, *et al.* Therapeutic effects and mechanisms of fecal microbiota transplantation on EAE partly through HPA axis-mediated neuroendocrine regulation. *Heliyon*. 2024; 10: e33214. <https://doi.org/10.1016/j.heliyon.2024.e33214>.
- [69] Zhi W, Li A, Wang Q, Yuan X, Qing J, Zhang C, *et al.* Safety and efficacy assessment of fecal microbiota transplantation as an adjunctive treatment for IgA nephropathy: an exploratory clinical trial. *Scientific Reports*. 2024; 14: 22935. <https://doi.org/10.1038/s41598-024-74171-4>.
- [70] Fenneman AC, Rampanelli E, van der Spek AH, Fliers E, Nieuwdorp M. Protocol for a double-blinded randomised controlled trial to assess the effect of faecal microbiota transplantations on thyroid reserve in patients with subclinical autoimmune hypothyroidism in the Netherlands: the IMITHOT trial. *BMJ Open*. 2023; 13: e073971. <https://doi.org/10.1136/bmjopen-2023-073971>.
- [71] Calabrese CM, Valentini A, Calabrese G. Gut Microbiota and Type 1 Diabetes Mellitus: The Effect of Mediterranean Diet. *Frontiers in Nutrition*. 2021; 7: 612773. <https://doi.org/10.3389/fnut.2020.612773>.
- [72] Lou Y, Wen X, Song S, Zeng Y, Huang L, Xie Z, *et al.* Dietary pectin and inulin: A promising adjuvant supplement for collagen-induced arthritis through gut microbiome restoration and CD4⁺ T cell reconstitution. *The Journal of Nutritional Biochemistry*. 2024; 133: 109699. <https://doi.org/10.1016/j.jnutbio.2024.109699>.
- [73] Moleón J, González-Correa C, Robles-Vera I, Miñano S, de la Visitación N, Barranco AM, *et al.* Targeting the gut micro-

- biota with dietary fibers: a novel approach to prevent the development cardiovascular complications linked to systemic lupus erythematosus in a preclinical study. *Gut Microbes*. 2023; 15: 2247053. <https://doi.org/10.1080/19490976.2023.2247053>.
- [74] Yin W, Liu M, Jin Z, Hao Z, Liu C, Liu J, *et al.* Ameliorative effects of insoluble dietary fiber and its bound polyphenols from adzuki bean seed coat on acute murine colitis induced by DSS: The inflammatory response, intestinal barrier and gut microbiota. *International Journal of Biological Macromolecules*. 2025; 286: 138343. <https://doi.org/10.1016/j.ijbiomac.2024.138343>.
- [75] Patel J, Kalantar-Zadeh K, Betz M, Joshi S. A Low-Protein, Plant-Dominant Gluten-Free Diet for Immunoglobulin A Nephropathy and Focal Segmental Glomerulosclerosis. *Advances in Kidney Disease and Health*. 2023; 30: 517–522. <https://doi.org/10.1053/j.akdh.2023.09.001>.
- [76] Groele L, Szajewska H, Szalecki M, Świdorska J, Wysocka-Mincewicz M, Ochocińska A, *et al.* Lack of effect of *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb12 on beta-cell function in children with newly diagnosed type 1 diabetes: a randomised controlled trial. *BMJ Open Diabetes Research & Care*. 2021; 9: e001523. <https://doi.org/10.1136/bmjdr-2020-001523>.
- [77] Matsuoka K, Uemura Y, Kanai T, Kunisaki R, Suzuki Y, Yokoyama K, *et al.* Efficacy of *Bifidobacterium breve* Fermented Milk in Maintaining Remission of Ulcerative Colitis. *Digestive Diseases and Sciences*. 2018; 63: 1910–1919. <https://doi.org/10.1007/s10620-018-4946-2>.
- [78] Straus Farber R, Walker EL, Diallo F, Onomichi K, Riley C, Zhang L, *et al.* A randomized cross-over trial of prebiotics and probiotics in multiple sclerosis: Trial feasibility, supplement tolerability and symptom abatement. *Multiple Sclerosis and Related Disorders*. 2024; 89: 105762. <https://doi.org/10.1016/j.msard.2024.105762>.
- [79] D T, Venkatesh MP. Fecal microbiota transplantation: History, procedure and regulatory considerations. *Presse Medicale*. 2023; 52: 104204. <https://doi.org/10.1016/j.lpm.2023.104204>.
- [80] Minkoff NZ, Aslam S, Medina M, Tanner-Smith EE, Zackular JP, Acra S, *et al.* Fecal microbiota transplantation for the treatment of recurrent *Clostridioides difficile* (*Clostridium difficile*). *The Cochrane Database of Systematic Reviews*. 2023; 4: CD013871. <https://doi.org/10.1002/14651858.CD013871.pub2>.
- [81] Janket SJ, Ackerson LK, Diamandis EP. Potential risks in fecal microbiota transplantation. *Clinical Chemistry and Laboratory Medicine*. 2020; 58: e95. <https://doi.org/10.1515/cclm-2019-1076>.
- [82] Belvončíková P, Macáková K, Tóthová N, Babál P, Tarabčáková L, Gardlík R. Investigating the Role of Gut Microbiota in the Pathogenesis and Progression of Rheumatoid Arthritis in a Collagen-Induced Arthritis Mouse Model. *International Journal of Molecular Sciences*. 2025; 26: 5099. <https://doi.org/10.3390/ijms26115099>.
- [83] Edwards V, Smith DL, Meylan F, Tiffany L, Poncet S, Wu WW, *et al.* Analyzing the Role of Gut Microbiota on the Onset of Autoimmune Diseases Using TNF^{ΔARE} Murine Model. *Microorganisms*. 2021; 10: 73. <https://doi.org/10.3390/microorganisms10010073>.
- [84] Armstrong HK, Bording-Jorgensen M, Santer DM, Zhang Z, Valcheva R, Rieger AM, *et al.* Unfermented β -fructan Fibers Fuel Inflammation in Select Inflammatory Bowel Disease Patients. *Gastroenterology*. 2023; 164: 228–240. <https://doi.org/10.1053/j.gastro.2022.09.034>.
- [85] Rodziewicz A, Szewczyk A, Bryl E. Gluten-Free Diet Alters the Gut Microbiome in Women with Autoimmune Thyroiditis. *Nutrients*. 2024; 16: 685. <https://doi.org/10.3390/nu16050685>.
- [86] Lam JKW, Cheung CCK, Chow MYT, Harrop E, Lapwood S, Barclay SIG, *et al.* Transmucosal drug administration as an alternative route in palliative and end-of-life care during the COVID-19 pandemic. *Advanced Drug Delivery Reviews*. 2020; 160: 234–243. <https://doi.org/10.1016/j.addr.2020.10.018>.
- [87] Trincado V, Gala RP, Morales JO. Buccal and Sublingual Vaccines: A Review on Oral Mucosal Immunization and Delivery Systems. *Vaccines*. 2021; 9: 1177. <https://doi.org/10.3390/vaccines9101177>.
- [88] González LF, Acuña E, Arellano G, Morales P, Sotomayor P, Oyarzun-Ampuero F, *et al.* Intranasal delivery of interferon- β -loaded nanoparticles induces control of neuroinflammation in a preclinical model of multiple sclerosis: A promising simple, effective, non-invasive, and low-cost therapy. *Journal of Controlled Release*. 2021; 331: 443–459. <https://doi.org/10.1016/j.jconrel.2020.11.019>.
- [89] Coppo R. A disease-modifying approach to the treatment of IgA nephropathy targeting mucosal IgA synthesis and beyond. *Kidney International*. 2023; 103: 258–261. <https://doi.org/10.1016/j.kint.2022.10.019>.
- [90] Yue L, Ye P, Zhang Y, Guo R, Xu W, Huang S, *et al.* An enhanced bioactive chitosan-modified microemulsion for mucosal healing of ulcerative colitis. *International Journal of Biological Macromolecules*. 2025; 284: 137847. <https://doi.org/10.1016/j.ijbiomac.2024.137847>.
- [91] Du G, Qin M, Sun X. Recent progress in application of nanovaccines for enhancing mucosal immune responses. *Acta Pharmaceutica Sinica B*. 2023; 13: 2334–2345. <https://doi.org/10.1016/j.apsb.2022.08.010>.
- [92] Saito E, Gurczynski SJ, Kramer KR, Wilke CA, Miller SD, Moore BB, *et al.* Modulating lung immune cells by pulmonary delivery of antigen-specific nanoparticles to treat autoimmune disease. *Science Advances*. 2020; 6: eabc9317. <https://doi.org/10.1126/sciadv.abc9317>.
- [93] Chen Y, Wu J, Wang J, Zhang W, Xu B, Xu X, *et al.* Targeted delivery of antigen to intestinal dendritic cells induces oral tolerance and prevents autoimmune diabetes in NOD mice. *Diabetologia*. 2018; 61: 1384–1396. <https://doi.org/10.1007/s00125-018-4593-3>.
- [94] Lee H, Khan N. Editorial: effectiveness and safety of vedolizumab in a matched cohort of elderly and non-elderly patients with inflammatory bowel disease - the IG-IBD LIVE study. *Alimentary Pharmacology & Therapeutics*. 2022; 56: 731–732. <https://doi.org/10.1111/apt.16957>.
- [95] Castillo-Álvarez F, Pérez-Matute P, Oteo JA, Marzo-Sola ME. The influence of interferon β -1b on gut microbiota composition in patients with multiple sclerosis. *Neurologia*. 2021; 36: 495–503. <https://doi.org/10.1016/j.nrleng.2020.05.006>.
- [96] Katz Sand I, Zhu Y, Ntranos A, Clemente JC, Cekanaviciute E, Brandstadter R, *et al.* Disease-modifying therapies alter gut microbial composition in MS. *Neurology(R) Neuroimmunology & Neuroinflammation*. 2018; 6: e517. <https://doi.org/10.1212/NXI.0000000000000517>.
- [97] Centanni L, Bencardino S, D'Amico F, Zilli A, Parigi TL, Allocca M, *et al.* Targeting mucosal healing in Crohn's disease: efficacy of novel pathways and therapeutic targets. *Expert Opinion on Therapeutic Targets*. 2024; 28: 963–978. <https://doi.org/10.1080/14728222.2024.2433124>.