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Review

Targeting Integrins in Immunity: Precision Matters for Therapeutic Interventions

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Abstract

Integrins are transmembrane receptors that mediate interactions between the extracellular matrix (ECM) and cells. Integrins are expressed as heterodimers composed of an α-subunit and a β-subunit. Based on several α-subunits and β-subunits present in mammals, each integrin receptor is functionally distinct with specific ligand-binding and signalling features. Upon activation, integrins regulate diverse cellular functions via the formation of multi-protein assemblies with intracellular signalling proteins at the cell surface. However, integrin dysfunction or aberrant activation is also associated with various pathophysiological consequences. Driven by extensive pre-clinical studies demonstrating integrins as potential therapeutic targets, many drug discovery strategies have already been attempted over the decades with limited success. Molecular complexity and functional redundancy of integrin subunits, along with the toxicity associated with global targeting, remain major hurdles for therapeutic applications, emphasising the need for further understanding of integrin biology. Emerging evidence supports an integrated role of integrins in both innate and adaptive immune systems. Integrins are involved in a diverse array of immunological functions, including leukocyte recruitment, pro-inflammatory signalling, macrophage polarisation, hematopoietic stem cell (HSC) homing, immune homeostasis, Toll-like receptor (TLR) signalling, beta-cell development and function, and immune checkpoint regulation. It has therefore become more apparent why dysregulation of these integrin-mediated functions is often linked to various diseases. Integrin signalling is driven by several crucial downstream kinases, including focal adhesion kinase (FAK), phosphoinositide 3-kinase (PI3K), proto-oncogene tyrosine-protein kinase Src (SRC), and integrin-linked kinase (ILK). Encouraging pre-clinical and clinical studies have demonstrated the translational prospects of targeting integrins indirectly via these downstream molecules. Considering the adverse side effects often resulting from the global targeting of integrins, precise targeting of integrin functions via an indirect or cell-type-specific approach may represent a promising direction for future therapeutic development.

Keywords: integrins; extracellular matrix; immunity; leukocytes; T cells; focal adhesion kinase (FAK); PI3K; integrin-linked kinase (ILK)

1. Introduction

Integrins are a large family of ubiquitously expressed, cell-adhesion transmembrane receptors that mediate interactions between the extracellular matrix (ECM) and cells, leading to the activation of multiple intracellular signalling pathways [1]. In mammals, integrins are expressed as heterodimers comprising an α-subunit and a β-subunit. A total of 18 α-subunits and 8 β-subunits are involved in the formation of 24 known heterodimers in mammals, showing functionally distinct ligand binding and signalling features [2]. While most subunits only form one kind of complex with one type of partner, the β1 subunit and the αv subunit can interact with more than one partner, and hence they are predominantly found in the majority of integrin heterodimers [3]. Integrins are dynamic signalling proteins that can relay signals in both directions across the plasma membrane based on their ability to reversibly switch between different conformations (Fig.1, Ref. [3]). The conformational changes are induced either by extracellular ligand binding (outside-in activation) or by interacting with the tightly regulated intracellular proteins (inside-out activation) via the integrin intracellular domains [4,5]. Integrins therefore enable cells to respond to both intracellular and extracellular changes.

2. Integrins in Health and Disease

Integrin activation forms large multi-protein assemblies at the cell surface via the recruitment of intracellular adaptors and signalling proteins. Integrin-driven signalling events regulate numerous cellular processes ranging from cell migration to cell proliferation, cell differentiation, cell survival, gene expression, as well as interactions with other receptor signalling such as growth factor receptors (GFRs) [6,7]. Specifically, cross-communications between integrin and GFRs are essential for the normal development process. For example, the integrin αvβ3 phosphorylates vascular endothelial growth factor receptor-2 (VEGFR-2) to facilitate the recruitment of bone marrow cells in angiogenic sites

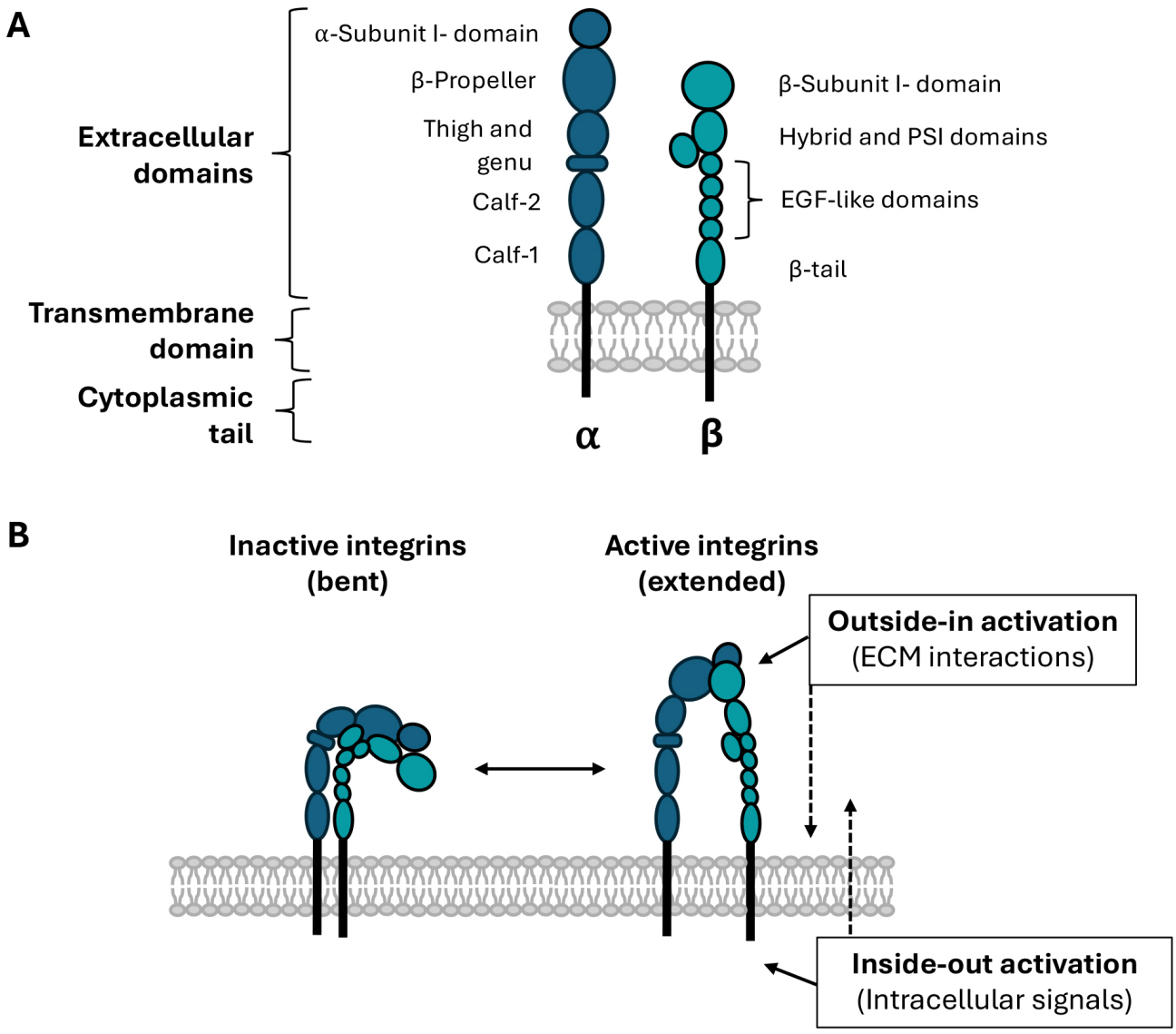

Fig. 1. Integrin structure and activation. (A) Domain architecture of integrin α and β subunits. (B) Conformational regulation of integrins on the cell surface. Integrins exist in a dynamic equilibrium between the bent conformation (inactive, with low affinity for ligand) and the extended conformation (active, with high affinity for ligand). Integrin activation can be initiated by extracellular matrix (ECM) interactions (outside-in activation) or intracellular signals (inside-out activation). Dotted lines indicate the direction of signals, originating from either extracellular or intracellular sources. EGF, epidermal growth factor; PSI, plexin/semaphorin/integrin. Both diagrams were adapted from reference [3].

[8]. During the development process, integrin also plays vital roles by regulating cell migration, rearrangement, and differentiation [9]. Given the indispensable involvement of integrin in many physiological functions, the consequences of its aberrant activation are also linked to numerous pathophysiological conditions. An elevated expression of integrins has been a common feature in multiple cancers. For example, integrins αvβ3, αvβ6, and α5β1, which are usually expressed at low levels in normal epithelia, can be highly upregulated in multiple tumours [10]. Moreover, integrin-mediated biological processes are often exploited by tumours to facilitate cancer progression, survival, and metastasis [11]. The impact of integrins in cancer progression has been extensively discussed elsewhere, along with therapeutic prospects of targeting integrins (refer to [1,12,13]). Apart from cancer, integrin is also implicated in other diseases including atherosclerosis, thrombosis, and fibrosis. The αvβ3 integrin stimulates an early atherogenic inflammation by activating flow-induced NF-κB activation [14]. Shear stress also activates matrix-binding integrins α5β1 and αvβ3 [15]. As the most abundant integrin in blood platelets, the αIIbβ3 integrin plays a critical role in arterial thrombosis [16]. Several integrins regulate tissue fibrosis, such as integrins αvβ5, αvβ6, and αvβ8, which are

expressed in both epithelial cells and fibroblasts, and can induce lung fibrosis by activating TGF-β [17,18]. Both α3 and α11 integrins also mediate kidney fibrosis by inducing fibroblast differentiation [19,20]. Based on the extensive role of integrins over a wide spectrum of pathophysiological conditions, integrins have been considered as potential therapeutic targets for decades.

3. Existing Barriers in Integrin-Targeting Interventions

Decades of investigations into the biological functions of integrins and their roles in human diseases have created opportunities for therapeutic development. Their exposure to the cell surface has also facilitated the exploration of integrins as attractive pharmacological targets for nearly 40 years. Numerous targeting strategies have been applied using small molecules, peptides, and monoclonal antibodies across a large number of clinical trials over the years. Small-molecule inhibitors constitute the largest class of integrin-targeting therapeutics, owing to several advantages related to cost, pharmacokinetic properties, and routes of administration. Many small-molecule drugs have been designed to target the Arg-Gly-Asp (RGD) motif, a tripeptide sequence that is highly conserved among numerous extracellular matrix (ECM) proteins and mediates binding to multiple integrin receptors [3]. However, most RGD-binding compounds ultimately failed as integrin inhibitors, as they were found to induce unfavorable ligand-mediated conformational changes that stabilize integrins in a high-affinity, activated state [3,21]. For example, αIIbβ3-integrin RGD mimetics (e.g., eptifibatide) and αvβ3-integrin RGD mimetics (e.g., cilengitide) exhibited agonist activity even at low concentrations. As an alternative strategy, non-RGD-based or more integrin-specific antagonists have been explored. Notably, the non-RGD mimetic RUC-1 and its more potent derivatives, RUC-2 and RUC-4, demonstrated promising therapeutic potential. In particular, RUC-4 was effective in inhibiting platelet aggregation and showed efficacy in the setting of coronary intervention [22,23]. Among monoclonal antibodies (mAbs) targeting integrins, several have demonstrated therapeutic efficacy in clinical trials. For instance, the αIIbβ3-integrin antibody abciximab proved effective in coronary interventions, while the α4-integrin antibody natalizumab showed clinical benefit in multiple sclerosis. In addition, antibodies targeting α4β7 integrin, such as vedolizumab and abrilumab, were effective in the treatment of Crohn's disease and ulcerative colitis [24]. Although both natalizumab and vedolizumab achieved regulatory approval, their clinical use has been associated with concerns regarding progressive multifocal leukoencephalopathy (PML), a rare but serious adverse event believed to be linked to inhibition of α4-containing integrins [21].

Despite many drug discovery projects and clinical studies focused on integrins, very few clinical trials have shown encouraging results, and toxicity remains a crucial issue in most cases. Considering significant efforts devoted to clinical trials over the decades, only a small number of agents received therapeutic approval [25,26]. The poor drug efficacy associated with integrin therapeutics is inherently linked to both the molecular and functional complexity of integrin subunits. Integrin functions are governed by a delicate balance between active and inactive states, mediated by conformational changes, protein–protein interactions, and trafficking [27]. Most of the failed integrin small-molecule inhibitors are capable of unfavourably inducing binding-mediated conformational shifts of integrin with high affinity [21,28]. The presence of the same subunit in multiple different integrins also poses a challenge in establishing selective, site-specific drugs. In addition, variable integrin expression levels represent another contributing factor to the existing challenges. For example, while a single cancer cell may express multiple types of integrins, their expression levels may differ from one cancer cell to another, depending on their interactions with the surrounding ECM proteins in the tumour microenvironment [29,30]. In addition, it also remains to be determined how the expression levels of integrins evolve through the course of tumour progression. Any hidden compensatory mechanism regulating integrin expression in tumours would even make it difficult for any integrin-targeting strategy to work. Perhaps, the major obstacle for integrin therapeutics is the existence of functional redundancy among integrins. For example, different integrin heterodimers may induce similar signalling activation and functions in cancer [31]. On the other hand, the same type of integrin can also perform contrasting roles at different stages of cancer development. For instance, the inhibition of β1 integrin represses breast tumour growth, but at the same time it also promotes metastasis by facilitating breast cancer cell invasion [32]. The integrin-targeting therapeutic expeditions over the decades have thus further emphasised a deeper understanding of integrin functions in health and disease.

4. Integrated Roles of Integrins in Immunity

Integrins play many regulatory functions within both innate and adaptive immune systems (Table 1, Ref. [33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64]). Among the integrin family subunits, the β2 integrin, also known as CD18, is exclusively expressed in leukocytes as a member of the leukocyte receptor subfamily of αβ integrins [33]. Based on variable α (CD11a-CD11d) subunits, the β2 subunit forms multiple heterodimeric surface receptors, such as lymphocyte function-associated antigen 1 (LFA-1, CD11a/CD18), macrophage-1 antigen (Mac-1, CD11b/CD18), αXβ2 (CD11c/CD18), and αDβ2 (CD11d/CD18), and these receptors are required for the leukocyte recruitment cascade [34,35]. Cell activation often upregulates the expression of all β2 integrins, followed

Table 1. Immune-modulating integrins.

Integrins	Expressing cells	Immune functions	Pathophysiological impacts	References
β2	Leukocytes	Leukocyte recruitment Anti-bacterial defense Immune homeostasis	Prevents LAD-1 Prevents bacterial infections Prevents autoimmunity	[33,34,35,37,38,39,40,41,42]
β1	Pancreatic beta-cells	Beta-cell proliferation Beta-cell function Insulin secretion	Prevents glucose intolerance Prevents impaired insulin secretion	[43,44,45,46]
α2β1, α5β1	Chondrocytes	Cartilage/collagen-specific pro-inflammatory cytokine & MMPs production	Promotes osteoarthritis	[47,48,49]
α3β1, α9β1	Neutrophils Macrophages DCs Monocytes	TLR activation Pro-inflammatory cytokine production	Promotes anti-microbial defense Prevents infections	[50,51,52,53]
α4β1, α4	Leukocytes HSCs	Leukocyte recruitment to CNS HSC homing to bone marrow	Promotes MS Limits excessive HSC in bloodstream	[54,55,56,57]
β4	Cancer epithelial cells	Anti-cancer immunity	Supports tumour progression	[58]
β6	Epithelial cells	Macrophage polarisation	Supports tumour progression	[36]
α4β7, β7	Leukocytes	Intestinal inflammation	Promotes UC and CD	[59,60]
αEβ7, αE	Lymphocytes	Cytotoxic T cell activation Regulatory T cell activation	Prevents cancer progression Prevents autoimmunity	[61,62,63,64]

LAD, leukocyte adhesion deficiency; MMP, matrix metalloproteinase; CNS, central nervous system; MS, multiple sclerosis; HSC, hematopoietic stem cell; UC, ulcerative colitis; CD, Crohn's disease; DCs, dendritic cells; TLR, Toll-like receptor.

by signal-dependent conformational changes controlling ligand affinity [65]. Being expressed in all leukocytes, activated LFA-1 engages with several cell surface proteins such as intercellular adhesion molecule 1–5 (ICAM-1–5), junctional adhesion molecule-1 (JAM-1), JAM-A, and endothelial cell-specific molecule-1 (ESM-1) [65,66,67]. Mac-1 is predominantly expressed in monocytes, macrophages, neutrophils and dendritic cells (DC), and binds not only to cell surface proteins including ICAM-1–4, vascular cell adhesion molecule-1 (VCAM-1), JAM-3, receptor for advanced glycation end products (RAGE), thymus cell antigen 1 (Thy-1, CD90), DC-specific ICAM-3-grabbing non integrin (DC-SIGN), and E-selectin [68,69,70,71,72], but also to matrix proteins such as fibronectin and collagen [73,74], plasma proteins such as matrix metalloproteinase-2 (MMP-2), MMP-9, fibrinogen, elastase as well as toll-like receptor-4 (TLR-4) ligand lipopolysaccharide (LPS) [75]. Furthermore, Mac-1 also acts as a receptor for complement, known as a complement receptor 3 (CR3), and facilitates the phagocytosis of complement-opsonized pathogens [76,77]. Macrophage polarisation is also regulated by the relative expression of CD11d. High expression of CD11d promotes pro-inflammatory macrophages, while its inhibition induces immune-suppressive macrophages and tumour progression [78]. The macrophage polarisation is also influenced by the β6 integrin expression in inflammatory epithelium as demonstrated in both inflammatory bowel disease (IBD) and colitis-associated cancer (CAC) in mice. The genetic deletion of β6 integrin resulted in diminished pro-inflammatory macrophage infiltration and polarisation, with reduced intestinal inflammation and tumour burden [36]. The cytokine expression in DCs is also regulated by the β2 integrin, as shown by a DC-specific β2 integrin knockdown in mice [37]. The critical role of β2 integrin in the immune system is emphasised by leukocyte adhesion deficiency (LAD) syndromes, driven by the β2 integrin deficiency [38]. LAD-1 patients carrying mutations in β2 integrins suffer from frequent and severe bacterial infections, due to impaired leukocyte adhesion and migration into the tissue as well as reduced pathogen-killing functions [39,40,41]. In addition, LAD-1 patients are also likely to suffer from autoimmune diseases such as IBD, type-1 diabetes, and nephritis [42]. This aberrant immune state of LAD-1 patients suggests that β2 integrins are essential not only to eradicate pathogens but also to prevent autoimmunity by maintaining immune homeostasis.

Alpha-E integrin, also known as CD103, forms a complete integrin heterodimer by binding with the β7 chain. CD103 is a widely used marker of tissue-resident immune cells in various organs [79] and is the only known integrin ligand for E-cadherin, a key adhesion protein expressed by epithelial cells [80]. CD103 expression in lymphocytes is induced by local transforming growth factor-β (TGF-β) production within the tissue microenvironment [81]. TGF-β signalling also promotes PI3K-driven phosphorylation of integrin-linked kinase (ILK), which mediates an 'inside-out' activation of CD103, and the subsequent activation of Akt downstream of PI3K/ILK signalling facilitates the

binding of CD103 to E-cadherin [82]. The cytolytic capacity of CD8 T cells is enhanced by CD103 since its interaction with E-cadherin leads to the polarization of lytic granules and the release of granzymes, facilitating the killing of E-cadherin-expressing cells [83,84]. CD103 expression in CD8+ tumour-infiltrating lymphocytes is therefore considered a favourable prognosis associated with increased overall survival [63]. However, apart from CD8 T cells, CD103 also acts as a co-stimulatory molecule for other lymphocyte subsets. For example, CD103 enhances the immunosuppressive capacity of Tregs in alleviating the symptoms of colitis, arthritis, and allergic contact hypersensitivity in animal models [61,62,64]. The enhanced immunosuppressive nature of CD103+ Tregs was also observed as a negative prognosis for patients with ovarian and breast cancer [85,86], owing to an undesirable consequence on tumour burden. Using mouse models of IBD, CD8+ CD103+ Tregs were identified with a capacity to ameliorate both TNF-mediated ileitis and T-cell-mediated colitis [87,88]. Genetic knockdown or antibody-mediated targeting of β7 integrin also plays a protective role in colitis [89,90], even though not only CD103 (αEβ7) but also α4β7 integrins are affected by it. Moreover, consistent with a connection between obesity and low levels of chronic inflammation, a high-fat diet downregulates CD103 expression in both CD4 T cells and γδ intraepithelial lymphocytes (IELs), resulting in a reduced persistence of IELs within the epithelial mucosa [91]. Given the multifunctional roles of CD103 in tissue-resident lymphocytes, further studies devoted to cell subset-specific analysis could decipher the therapeutic implications for targeting CD103.

The α4β1 integrin plays an indispensable role in leukocyte recruitment to the inflamed central nervous system (CNS) in experimental autoimmune encephalomyelitis (EAE), a murine model of multiple sclerosis (MS) [57]. The leukocyte adhesion in the CNS is mediated by interaction between α4β1 integrin expressed on leukocytes and vascular cell adhesion molecule (VCAM)-1 expressed in the CNS. In addition, the α4β1 integrin expression on hematopoietic stem cells (HSCs) has been shown to be necessary for HSC homing. Its interaction with VCAM-1 on endothelial cells within the bone marrow niche facilitates the retention of HSC in the bone marrow [55]. A genetic deletion of α4 integrin in mice resulted in elevated levels of HSC in the bloodstream compared to wild-type controls [56], emphasising a critical role of α4 in HSC biology. A similar outcome was also observed in mice with the VCAM-1 antagonist Bortezomib [54].

The integrin α5β1 is involved in the pathogenesis of osteoarthritis (OA), which is triggered by an imbalance between cartilage ECM synthesis and degradation. The activation of α5β1 in cartilage tissue, particularly in chondrocytes, is associated with the elevation of several pro-inflammatory factors, such as IL-1β, TNF-α, and NO, playing a critical role in the early stage of OA [49]. The integrin α5β1 also induces both reactive oxygen species (ROS) and matrix metalloproteinase-13 (MMP-13), via the binding of the fragmented fibronectin derived from damaged cartilage [47]. The integrin α2β1, a type I collagen receptor, is also expressed in arthritic chondrocytes but not in normal adult chondrocytes [48]. Like α5β1, the integrin α2β1 is synergistically associated with pro-inflammatory cytokines and MMP production, thereby facilitating the pathogenesis of OA [49].

Integrins are a crucial point of target for pathogens for adherence to as well as for invading host cells. As a result, integrins are also linked to Toll-like receptors (TLRs), a crucial first-line defence of the innate immune system. For example, α3β1 integrin, also known as Very Late Antigen (VLA)-3 or CD49c/CD29, is involved in the endocytosis of the TLR2 ligand Pam3CSK4, thereby facilitating its recognition and the subsequent activation of TLR1/2 signalling within the endosome. Increased α3β1 expression on neutrophils has been associated with pro-inflammatory phenotypes during sepsis, and the TLR2-induced inflammatory responses in neutrophils were attenuated by α3β1 deficiency [52]. The TLR-induced pro-inflammatory cytokine production in macrophages and DCs is enhanced by the CD18 (β2) deletion, suggesting a β2-mediated regulation of TLR response [53]. The TLR ligation-induced reactive oxygen species (ROS) production also mediates β2 integrin activation on myelomonocytes and subsequent leukocyte adhesion [50]. The α9β1 integrin, in synergy with TLR2 and TLR4, induces both macrophages and DCs to facilitate functional activation of Th17 cells during arthritis [51].

Given the well-documented influence of ECM on beta-cell development and function in islets [92], integrins, particularly β1-integrin receptors, play critical roles in beta-cell adhesion and functions. A beta cell-specific KO of β1-integrin in mice resulted in diminished beta-cell mass due to a lack of cell proliferation and impaired insulin secretion [43]. A postnatal KO of beta cell-specific β1-integrin induced similar phenotypes, including decreased beta cell mass, glucose intolerance, and impaired insulin secretion [44]. In accordance with animal studies, blockade of β1-integrin in humans leads to impaired differentiation and elevated apoptosis of beta cells [46]. It has been shown that focal adhesion kinase (FAK) activation induced via the ECM and β1-integrin interaction mediates glucose-stimulated insulin secretion [45].

Mounting evidence suggests that integrins are closely related to anti-cancer immunity by regulating TGF-β activation [93]. Recent studies have shown several promising prospects for integrin-targeted immunotherapy. Targeting integrins could have a significant impact on the tumour microenvironment (TME) by enhancing PD-1/PD-L1 therapeutic efficiency, suppressing TGF-β secretion in the TME, and promoting cytotoxic T cells. For example, β4 integrin-targeting immunological approaches, using ei-

ther β4 integrin-pulsed DCs for vaccination or the adoptive transfer of anti-CD3/anti-β4 bispecific antibody-armed tumour-draining lymph node T cells, not only showed anti-tumour effects but also enhanced the efficacy of a PD-L1 inhibitor in immunocompetent mouse models of mammary tumours and head and neck squamous cell carcinoma [58].

5. Targeting the Immune-Modulating Functions of Integrins

The promising implication of α4β1 integrin in an *in vivo* MS model prompted the development of Natalizumab, a monoclonal antibody directed against α4, blocking α4β1 integrin. Natalizumab was approved as the first targeted therapy for the treatment of relapsing-remitting MS [94]. Both Vedolizumab, a humanised monoclonal antibody that selectively targets α4β7, and Etrolizumab, a humanised monoclonal antibody against β7 integrin, were also proven to be effective for the treatment of moderate-to-severe ulcerative colitis (UC) and Crohn's disease (CD) [59,60]. However, Etrolizumab, failed to maintain consistent results in a Phase 3 trial [95]. Another anti-α4β7 antibody, Abrilumab, demonstrated efficacy in patients with UC in a Phase 2 study [96], but failed in a Phase 2b study in CD due to the lack of clinical remission [96].

Considering the critical role of β2 integrins in leukocyte recruitment, therapeutic targeting of β2 integrins has been attempted using Efalizumab, an LFA-1 monoclonal antibody, to treat inflammatory diseases [97]. However, the outcomes were far from satisfactory due to severe side effects, including bacterial sepsis and viral meningitis, which resulted in a withdrawal from the market. The inherent drawback associated with a pan-β2 targeting is linked to its divergent functions in a cell type-specific manner. The outcomes are therefore a consequence of a systemic modulation of β2 integrins, and it is also a common scenario for many immune-modulating integrins as well. In addition, variable expression intensity and ligand affinity of these integrins across cell types pose further complications for therapeutic interventions.

Since integrin functions are precisely modulated by several crucial downstream kinases such as FAK, PI3K, SRC, and ILK [98], a number of studies have been devoted to the indirect targeting of integrins by focusing on these signalling molecules. For example, FAK inhibition was shown to prevent uterine serous carcinoma (USC) cell growth *in vivo* [99] and promote anti-tumour immune response by enhancing T cell co-stimulatory pathway [100]. Several FAK inhibitors alone or in combination have already entered clinical trials [13]. While all FAK inhibitors were well-tolerated, only modest efficacy was observed in a few studies. Among integrin downstream molecules, PI3K inhibitors have been the most effective in clinical settings, and some of them were approved for cancer treatment [13]. For example, Alpelisib, a PI3Kα inhibitor, was approved by the U.S. Food and Drug Administration (FDA) in 2019 for breast cancer patients who have a PIK3CA mutation [101]. Dasatinib, a potent SRC inhibitor, has also been approved for the treatment of chronic myeloid leukemia [13]. Further clinical studies with Dasatinib showed encouraging outcomes for breast cancer patients [102,103].

A number of pre-clinical studies recognised ILK as a potential therapeutic target and demonstrated the efficacy of several small-molecule ILK inhibitors for various cancers [104,105,106,107,108,109]. While the functions of ILK have been mostly characterized in non-immune cells, several published reports have indicated an immunomodulatory role for ILK. For example, ILK was shown to play a pivotal role in activating LFA-1 and its recognition of ICAM-1 for neutrophil recruitment into tissues, indicating a mechanism for the ILK–LFA-1 signalling in mounting an inflammatory response [110]. ILK overexpression is associated with the up-regulation of lymphoid enhancer factor-1 (LEF-1), which in cooperation with T cell factor-1 (TCF-1), plays important roles in T cell development [111,112], indicating the relevance of ILK to T cell activation. My earlier observations identified ILK as a pro-inflammatory molecule regulating NF-κB p65 Ser536 phosphorylation and TNF-α synthesis via both PI3K/AKT-dependent and -independent manner based on the stimulus [113]. Using mice deficient in myeloid-specific ILK, my earlier research findings demonstrated an essential role of myeloid-ILK in mediating intestinal inflammatory signalling during experimental colitis [114], as well as in promoting colon tumorigenesis in both colitis-associated and APCmin/+-driven mouse models of colorectal cancer (CRC) [115]. The reduced tumour burden in the myeloid-ILK-deficient mice with enhanced intra-tumoral infiltration of CD8 T cells. An elevated tumour infiltration of ILK+ myeloid cells was also observed in CRC tissue microarrays compared to their adjacent normal sections, suggesting a conserved role for myeloid-ILK in CRC development [115]. Further investigations driven by our earlier work also showed a correlation between ILK expression and immunosuppressive TME markers, including different immune checkpoints. In particular, ILK was required for PD-L1 expression in CRC cell lines and ILK deficiency sensitised CRC cell lines to immune cell cytotoxicity, suggesting an immunomodulatory role of ILK expression in tumour cells [116]. These observations not only emphasised the therapeutic potential of targeting integrins indirectly via signalling molecules but also signified cell type-specific approaches as viable options (Fig. 2), facilitating the fine-tuning of integrin functions.

6. Cell Type–Specific Targeting: A Promising Strategy for Integrin-Directed Therapeutics

The lack of sustained therapeutic efficacy and the presence of associated systemic toxicity remain major challenges in the development of integrin-directed therapeutics. Consequently, precise cell-type–specific strategies are re-

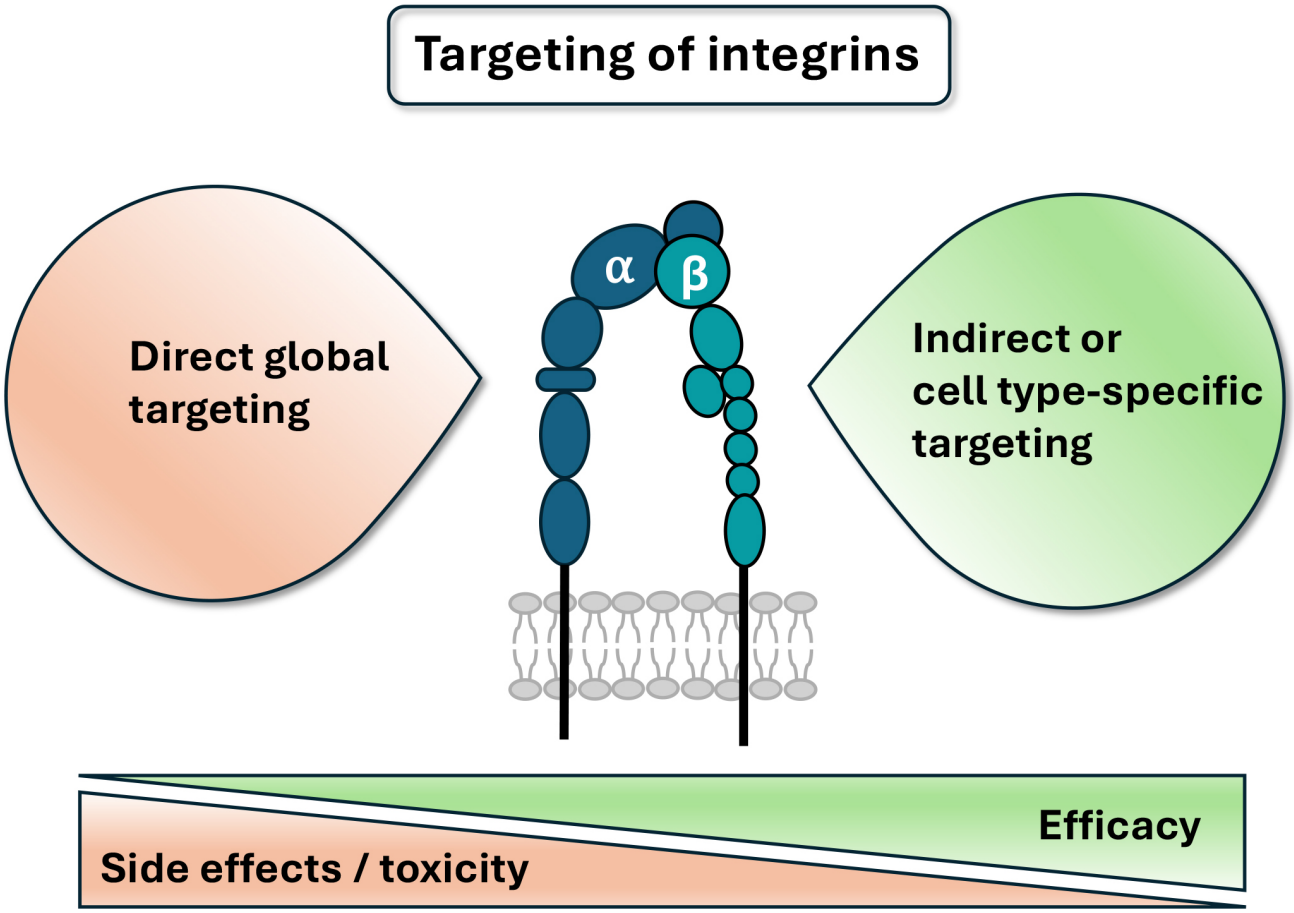

Fig. 2. Integrins targeting strategies. Integrins can be directly targeted globally, indirectly via integrin-associated signalling molecules or via a cell type-specific manner. Global targeting strategies have been attempted for decades, showing limited efficacy with severe side effects. On the other hand, both indirect targeting via signalling molecules and cell type-specific targeting have shown potential for therapeutic efficacy with limited side effects.

quired to ensure on-target efficacy at the cellular level while minimizing adverse effects arising from off-target interactions. Several cell-type-specific targeting strategies based on the incorporation of ligands or antibodies specific to defined cell populations have been explored in preclinical studies. Given that RGD-binding integrins (e.g., α5β1 and αv) are well-validated tumour-associated antigens owing to their overexpression in many tumours, including the tumour vasculature [10,117], RGD peptides have been employed as conjugates with liposomes, polymeric nanoparticles, or viral capsids to selectively target these integrins on activated endothelial cells during tumour-induced angiogenesis [118]. Cell-type-specific targeting strategies have been extensively explored in preclinical studies of CNS disorders, which remain a major clinical challenge. This is not only due to the blood-brain barrier (BBB) limiting therapeutic penetration into the brain but also because improving drug efficacy requires targeting endothelial cells within the CNS [119]. To enhance cell-specific targeting in the CNS, endothelial transporter-specific ligands are often incorporated into therapeutic agents to facilitate receptor-mediated transcytosis across the BBB endothelium. Among these, integrin αvβ3 (the RGD receptor) has also attracted interest as a potential endothelium-specific CNS target [120], alongside other receptors such as the transferrin receptor (TfR) [121], the insulin receptor [122], and the low-density lipoprotein receptor-related protein-1 (LRP1) [123]. To enhance therapeutic accumulation following entry into the CNS, dual-targeting strategies have also been explored by incorporating ligands that interact with additional cell types within the CNS, alongside endothelial transporter–specific ligands. For example, combining TfR, which is highly expressed on BBB endothelial cells, with tumour-specific receptors such as the folate receptor or the TAT receptor has been shown to increase therapeutic uptake by brain tumour cells and improve survival compared with single-targeting approaches [121,124]. Integrins have also been exploited as targets for antibody Fc effector functions in cancer immunotherapy through dual-targeting strategies. For example, an engineered mouse serum albumin–IL-2 fusion with an extended serum half-life, designed to activate $CD8^+$ T cells and NK cells, was combined with an Fc fusion to

an engineered RGD-containing peptide (2.5F). This construct elicited significant protective antitumour responses in mouse tumour models [125].

7. Concluding Remarks

Most integrin-based therapeutic strategies are focused on disrupting ligand-integrin interactions. Considering the complexity associated with integrin activation and functions, drugs targeting integrin receptor conformations or relevant signalling molecules are more effective approaches for clinical perspective. Since adverse side effects constitute a major obstacle for most integrin-selective interventions, indirect targeting of integrins via signalling molecules represents an achievable alternative option to avoid toxicity. In addition, given that most animal studies have been designed with a global knockout or inhibition, pre-clinical studies could also be more tailored not only to indirect approaches but also to cell type-specific focus (Fig. 2). For cell type–specific dual-targeting approaches, careful selection of targeting ligands is critical to ensure the consistent preservation of their individual targeting activities. Moreover, a comprehensive understanding of their synergistic interactions, particularly the mechanisms by which two ligands can be jointly integrated to enhance specificity toward a single cell type, is essential for the rational design of improved therapeutics.

It has become increasingly evident that integrins are intricately linked to many immune functions and immune disorders. Hence, extensive cell type-specific investigations could unravel further insights about the impact of integrins on the dynamics of immunity, which could potentially lead to much-needed interventions to fine-tune integrins at the cellular level. Moreover, further exploration is indeed required for a comprehensive understanding of integrin regulators, including both upstream and downstream effectors. A detailed molecular analysis of integrins for each clinical circumstance could pave the way to precise and efficacious interventions in the future.

Author Contributions

AUA single-handedly performed all literature search, conceived the draft outlines, drafted the manuscript, revised the manuscript and prepared figures. AUA also single-handedly contributed to all editorial changes as a part of the revision process. AUA read and approved the final manuscript. AUA agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The author is an employee of Aeterna Health Services Pty Ltd. The judgments in data interpretation and writing were not influenced by this relationship. The author declares no conflict of interest.

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