

# $\alpha 4$ Integrins in Immune Homeostasis and Disease



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**Abstract**  $\alpha 4$  integrins (including  $\alpha 4\beta 1$  and  $\alpha 4\beta 7$ ) are primarily expressed on leukocytes. By interacting with their ligands expressed on high endothelial venules (HEVs),  $\alpha 4$  integrins mediate the recruitment of leukocytes from blood circulation to lymphoid organs and inflamed tissues, thereby playing essential roles in immune surveillance and host defense. The function of integrins is dynamically regulated by their activation and signaling. Integrin activation is associated with global conformational rearmament from a bent to extend conformation, mainly triggered by intracellular activation signals, termed “inside-out” signaling. The ligand binding to the integrin can also activate multiple intracellular pathways, which is termed “outside-in” signaling. In this chapter, we summarize the major findings regarding  $\alpha 4$  integrins over the last decades, including their structures, extracellular ligands, intracellular adaptor proteins, and functions in homeostasis and diseases, including cancer, multiple sclerosis (MS), inflammatory bowel disease (IBD), and other autoimmune diseases.

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## 1 Introduction

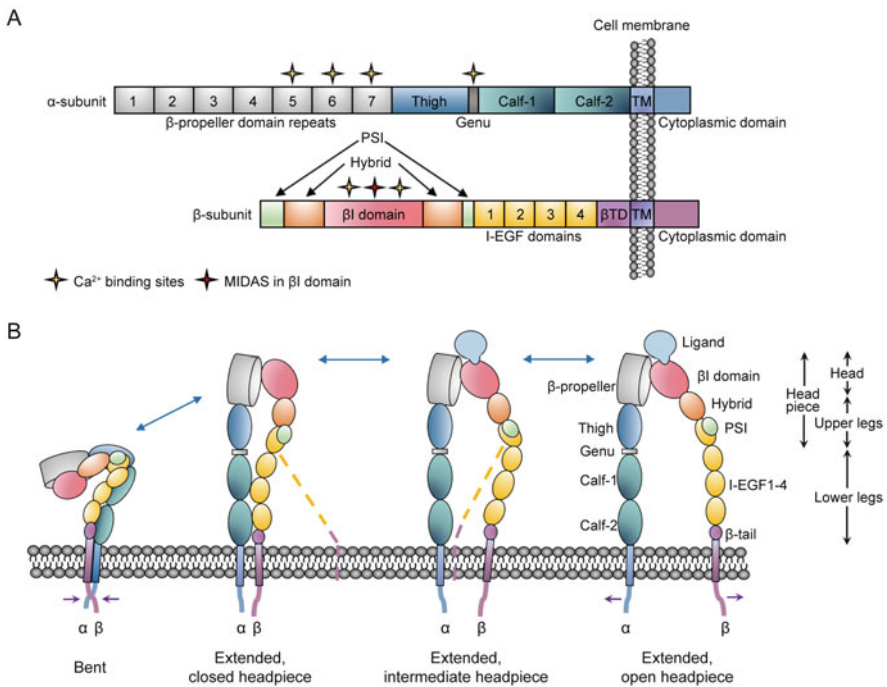
Integrins are a family of  $\alpha/\beta$  heterodimeric cell adhesion molecules, which exist extensively in all multicellular organisms (Hynes 1987; Tamkun et al. 1986). They were named “integrins” because they are integral membrane protein complexes for cell adhesion to the extracellular matrix (ECM) and were first proposed in the 1980s at the molecular level (Hynes 1987; Tamkun et al. 1986). Integrins have been major cell adhesion receptors since the early evolutionary history of the metazoans (Burke 1999; Hughes 2001), and homologous integrin sequences are even found in many prokaryotes (Johnson et al. 2009), suggesting they are a conserved evolutionary process and have pivotal functions in a wide range of scenarios. The vertebrate integrin family originates from homologous domains residing in the protists and prokaryotes, adapting itself to diverse functions within complete immune and closed circulatory systems throughout chordate evolution from lower organisms to individuals of phylum Chordata (Johnson et al. 2009). In vertebrates, 18 integrin  $\alpha$  subunits and 8  $\beta$  subunits form at least 24 different integrins (Hynes 2002). These integrins form a superfamily of cell adhesion receptors that bind to ECM ligands, cell-surface-expressing ligands, and pathogenic ligands and are responsible for mediating cell–matrix attachments, cell–cell and cell–pathogen interactions.

Integrin  $\alpha 4\beta 1$ , also named very late activation antigen-4 (VLA-4), and CD49d/CD29 were described approximately 30 years ago (Hemler et al. 1987a) as a new member of the VLA antigen proteins that were originally found to appear during late T-cell activation (Hemler et al. 1985). Integrin  $\alpha 4\beta 1$  facilitates the recruitment of leukocytes to endothelial cells upon inflammation through the interaction with its ligand, vascular cell adhesion molecule-1 (VCAM-1) (Elices et al. 1990). Furthermore, the  $\alpha 4\beta 1$ –VCAM-1 axis in different connective tissue cells has fundamental roles in many physiological processes, such as tissue organization, angiogenesis, and heart and skeleton development (Bouvard et al. 2001; Yong and Khwaja 1990). Integrin  $\alpha 4\beta 1$  on lymphocytes also recognizes the fibronectin (FN) Type III connecting-segment-1 (CS-1) region during T-cell function execution and immune responses (Wayner et al. 1989b). Soon after the discovery of integrin  $\alpha 4\beta 1$ , another  $\beta$  integrin subunit named  $\beta 7$  was reported to form heterodimers with the  $\alpha 4$  integrin subunit in mice (Holzmann and Weissman 1989; Kilshaw and Murrant 1991) and humans (Erle et al. 1991). Integrin  $\alpha 4\beta 7$  (lamina propria-associated molecule-1, LPAM-1; CD49d/ $\beta 7$ ), whose distribution is restricted to subsets of immune cells in peripheral blood, mediates adhesion to mucosal tissues, such as gut-associated lymphoid tissue (GALT) through binding to its primary ligand, mucosal addressin cell adhesion molecule-1 (MAdCAM-1) (von Andrian and Mackay 2000; Yu et al. 2012).  $\alpha 4\beta 1$  and  $\alpha 4\beta 7$  share some ligands, including VCAM-1 and FN.  $\alpha 4\beta 7$  exhibits preferential binding to MAdCAM-1 over the other two ligands (Yu et al. 2012). Moreover, integrin  $\alpha 4\beta 7$  can bind to human immunodeficiency virus-1 (HIV-1) envelope glycoprotein gp120 to mediate an HIV–T-cell interaction, thereby participating in HIV-1 infection of T cells (Arthos et al. 2008; Liu and Lusso 2020; Wang et al. 2021).

Overall, α4 integrins play critical roles in multiple biological and pathological processes, including leukocyte recruitment from the bloodstream into lymphoid organs and targeted tissues, immune cells, especially T-cell co-stimulation, and embryonic development.

## 2 Structure of α4 Integrins

Integrins are α/β heterodimeric type I transmembrane proteins. Both α and β subunits consist of a large extracellular domain, a single transmembrane domain, and a short cytoplasmic domain (Fig. 1a) (Arnaout et al. 2005). In humans, the α4 subunit contains 1032 amino acid residues, and both β1 and β7 subunits contain 798 amino acid residues. Since the first characterization of the integrin α4 subunit in 1989, many studies have shed light on the structure of α4 integrins (Baldini and Cro 1994; Kassner et al. 1992; Wang et al. 2018; Yu et al. 2012).



**Fig. 1** Schematic of the α4 integrin structure and conformational rearrangements. (a) Domains within the primary structure of α- and β-subunits of α4 integrin are shown. Yellow and red asterisks denote Ca<sup>2+</sup>- and Mg<sup>2+</sup>-binding sites, respectively. (b) Conformational rearrangements of the α4 integrin during activation. Broken lines symbolize lower leg flexibility. Redrawn from Zhang and Chen (Zhang and Chen 2012)

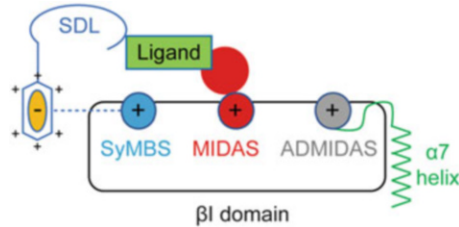
## 2.1 Extracellular Domain

Integrin  $\alpha 4$  subunit, which contains five extracellular domains, including a seven-bladed  $\beta$ -propeller, a thigh, a genu, and two calf domains, belongs to the  $\alpha$ -I less integrin family because it lacks an I domain inserted between blades 2 and 3 in the  $\beta$ -propeller domain (Fig. 1a) (Larson et al. 1989). For the  $\beta 1$  and  $\beta 7$  subunits, the extracellular domain consists of a  $\beta$ I ( $\beta$ A), hybrid, plexin-semaphorin-integrin (PSI), cysteine-rich integrin epidermal growth factor (I-EGF) 1–4, and  $\beta$ -tail domains (Fig. 1a) (Xiao et al. 2004; Yu et al. 2012).

The conformations and dimensions of several integrin ectodomains (e.g.,  $\alpha$ X $\beta$ 2,  $\alpha$ V $\beta$ 3, and  $\alpha$ I**b $\beta$ 3) have been extensively studied by different research groups (Xie et al. 2010; Xiong et al. 2001; Zhu et al. 2008a). The overall shape of the integrin extracellular domain is a large “head” on two long “legs” with flexible “knees” (Fig. 1b). In 2012, the structure of the integrin  $\alpha 4\beta 7$  ectodomain was revealed by electron microscopy (EM) and X-ray crystal structure (Yu et al. 2012). The integrin “head piece” contains a  $\beta$ -propeller domain and  $\beta$ I domain, together with the “upper leg,” which contains an  $\alpha$  thigh and  $\beta$  hybrid, PSI, and I-EGF1 domains (Yue et al. 2013). The remaining calf-1/2, I-EGFs, and  $\beta$ -tail domains in the ectodomain make up the “lower leg” of the integrin (Fig. 1b) (Yu et al. 2012).**

The adhesion between an  $\alpha 4$  integrin and its ligand is metal ion-dependent. In the  $\alpha 4$  subunit, there are three  $\text{Ca}^{2+}$ -binding sites located in the loops extending between propeller blades 5 to 7 and one site located at the “genu” (Fig. 1a). The  $\beta$ -propeller  $\text{Ca}^{2+}$ -binding sites are involved in the regulation of the integrin-ligand binding affinity. Conservative mutations in these sites of the  $\alpha 4$   $\beta$ -propeller significantly decreased the affinity for ligand binding to  $\alpha 4\beta 1$  (Masumoto and Hemler 1993).

In the  $\beta 1$  and  $\beta 7$  subunits, the  $\beta$ I domain contains an interlinked linear array of three metal ion-binding sites, with a metal ion-dependent adhesion site (MIDAS) at the center flanked by two other sites: the synergistic metal ion-binding site (SyMBS) and the adjacent to MIDAS (ADMIDAS). Based on the electron density in crystal structures, MIDAS is occupied by  $\text{Mg}^{2+}$ , but the two flanking sites are loaded with  $\text{Ca}^{2+}$  (Zhu et al. 2008b). The divalent cation in the MIDAS site forms a critical interaction with a negatively charged residue, usually Asp, in the integrin ligand. Disruption of the MIDAS site by mutations completely abolished the MAdCAM-1 binding to integrin  $\alpha 4\beta 7$  (Chen et al. 2003). SyMBS, also termed ligand-associated metal-binding site (LIMBS), exhibits a positive regulatory effect for integrin-ligand binding, which is required for the activation of  $\alpha 4\beta 7$  (Chen et al. 2003). The SyMBS metal ion can form a cation- $\pi$  interaction with a conserved aromatic residue (Tyr or Phe) in the specificity-determining loop (SDL), which may help to stabilize SyMBS metal ion coordination and maintain the proper conformation of SDL for an integrin high-affinity state (Pan et al. 2010; Zhang and Chen 2012) (Fig. 2). When occupied by  $\text{Ca}^{2+}$ , ADMIDAS functions as a negative regulatory site responsible for keeping the integrin in the low-affinity state by preventing the downward movement of the  $\beta$ I domain C-terminal  $\alpha 7$ -helix, a critical step in integrin activation.  $\text{Mn}^{2+}$  can compete with  $\text{Ca}^{2+}$  to occupy the ADMIDAS site and induce integrin activation by the release



**Fig. 2** Metal ion cluster in the  $\beta I$  domain. The linear cluster of the  $\beta I$  domain metal ion-binding sites is shown as SyMBS, MIDAS, and ADMIDAS from left to right. The metal ion-binding sites are colored as follows: blue, SyMBS; red, MIDAS; gray, ADMIDAS. The cation- $\pi$  interaction between the SyMBS metal ion and the aromatic side chain of Tyr or Phe is shown by a blue dashed line

of the inhibitory effects of  $\text{Ca}^{2+}$  (Chen et al. 2004; Humphries et al. 2003) (Fig. 2). The downward displacement of the  $\beta I$  domain C-terminal  $\alpha 7$ -helix allosterically alters the geometry of the metal ion clusters in a way that increases the affinity for ligand binding (Zhang and Chen 2012) (Fig. 2).

## 2.2 Transmembrane Domains

The integrin  $\alpha$  and  $\beta$  subunits anchor themselves within the cell plasma membrane via a single short transmembrane domain (TMD) (Fig. 1a). In addition to connecting the integrin extracellular domain and cytoplasmic domain, TMD has an important role in transducing bidirectional signaling across the plasma membrane (Kim et al. 2003). The linkers between the integrin ectodomain and TMD helices are suggested to be quite flexible during integrin activation, facilitating the  $\beta$  hybrid domain swing-out and overall conformational shift of the integrin molecule to a high-affinity conformation (Lau et al. 2009). Acidic phospholipids in the plasma membrane may ionically interact with the integrin intramembrane basic residue (K/R) close to the TMD and cytoplasmic domain border, which is believed to stabilize the integrin transmembrane dimer and hold the integrin in a resting state (Kim et al. 2011; Lu et al. 2016b). Intriguingly, calcium ions ( $\text{Ca}^{2+}$ ) may disrupt the ionic K/R–lipid interaction through its positive charge, which leads to the separation of the integrin  $\alpha/\beta$  TMDs and the subsequent extracellular domain extension to a high-affinity conformation (Guo et al. 2018).

## 2.3 Cytoplasmic Domains

The integrin cytoplasmic domain is very short. The  $\alpha 4$  and  $\beta 1/\beta 7$  subunits have approximately 30 and 50 amino acid residues, respectively. It serves as a vital bond

connecting its mechano-sensing ectodomain with its cytoplasmic adaptor proteins within the cell (Legate et al. 2006; Wiesner et al. 2006). The binding proteins for the  $\beta$  subunit cytoplasmic domain have been well characterized (Harburger and Calderwood 2009; Zaidel-Bar et al. 2007). For example, talin binds to the membrane-proximal NPxY motif via its canonical phosphotyrosine-binding (PTB) domain, which is critical for integrin activation (Calderwood et al. 2003; Wegener and Campbell 2008). Kindlin binds to a serine/threonine (S/T) rich motif and the membrane-distal NxxY motif, which functions as an integrin co-activator (Calderwood et al. 2003; Wegener and Campbell 2008). Some other PTB-containing proteins, such as docking protein 1 (DOK1) and integrin cytoplasmic domain associated protein 1 (ICAP1), suppress integrin activation by competition with talin (Liu and Boggon 2013; Wegener et al. 2007). Although filamin has no PTB domain, it also competes with talin/kindlin for binding to the  $\beta$  tail because of the overlapping binding sites in the integrin  $\beta$  tail (Calderwood et al. 2013b). The adaptor proteins for the  $\alpha 4$  tail are less well studied. Integrin inhibitors, such as mammary-derived growth inhibitor (MDGI) and SHANK-associated RH domain-interacting protein (SHARPIN), interact with the  $\alpha 4$  cytoplasmic domain around the conserved juxtamembrane GFFKR motif (Bouvard et al. 2013). The GFFKR motif serves as an important intrinsic structural component in making a salt bridge between the  $\alpha/\beta$  cytoplasmic tails to keep the integrin inactive (Lu et al. 2001). Paxillin specifically binds to the  $\alpha 4$  tail and regulates cell spreading and migration (Liu and Ginsberg 2000; Liu et al. 2002; Liu et al. 1999). Moreover, a study using chimeric  $\alpha 2$ ,  $\alpha 4$ , and  $\alpha 5$  integrins demonstrates that the cytoplasmic tails of different  $\alpha$  subunits contribute to the determination of integrin-ligand binding specificity (Chan et al. 1992).

### 3 Extracellular Ligands for $\alpha 4$ Integrins

#### 3.1 VCAM-1

The cell-surface glycoprotein VCAM-1 belongs to the Ig superfamily (IgSF) and contains seven Ig-like extracellular domains or is alternatively spliced into six or eight Ig-like domains (Renz et al. 1994). VCAM-1 is widely expressed on the stimulated endothelial cells of blood vessels, peripheral lymph nodes (PLNs), and bone marrow (BM) (Berlin-Rufenach et al. 1999). Both integrin  $\alpha 4\beta 1$  and  $\alpha 4\beta 7$  can bind to VCAM-1. Domain 1 (D1) and domain 4 (D4) of VCAM-1 contribute to  $\alpha 4\beta 1$ -dependent adhesion (Osborn et al. 1992). The linear sequence for QIDSPL, especially the tripeptide IDS (Ile-Asp-Ser), in the D1 and D4 has been demonstrated to be critical for  $\alpha 4\beta 1$  recognition (Baiula et al. 2019; Vonderheide et al. 1994). It is noteworthy that both the resting and activated integrin  $\alpha 4\beta 1$  can bind to VCAM-1 D1, whereas only the activated  $\alpha 4\beta 1$  can bind to VCAM-1 D4 (Kilger et al. 1995). Similarly, integrin  $\alpha 4\beta 7$  can also bind to D1 and D4 of VCAM-1 (Ruegg et al. 1992) but with much less affinity than  $\alpha 4\beta 1$ .

### 3.2 *MAdCAM-1*

MAdCAM-1, an IgSF type I transmembrane glycoprotein, is the primary ligand for integrin  $\alpha$ 4 $\beta$ 7. MAdCAM-1 is specifically expressed on the endothelium of HEVs in the gut and GALT, such as Peyer's patches and MLNs, and the venules of the lamina propria (LP) (Berlin et al. 1995; Cox et al. 2011; Springer 1994). The interaction between integrin  $\alpha$ 4 $\beta$ 7 and MAdCAM-1 has an essential role in supporting gut-targeting lymphocyte homing. MAdCAM-1 consists of two Ig-like domains, a mucin-like region, a short TMD, and a cytoplasmic domain (Shyjan et al. 1996). Structural analysis of the MAdCAM-1- $\alpha$ 4 $\beta$ 7 complex has revealed that  $\alpha$ 4 $\beta$ 7 directly binds to MAdCAM-1 aspartate 42 (Asp42) located on the protruding CD loop in Ig domain 1 through the MIDAS site located in the  $\beta$ 7 I domain (Tan et al. 1998; Yu et al. 2012). Moreover, a D strand in the I1 set of MAdCAM-1 Ig domain 2 is also necessary for  $\alpha$ 4 $\beta$ 7 recognition and binding (Newham et al. 1997; Tan et al. 1998). The mucin-like domain, which is a serine/threonine-rich region, leads to a more upright conformation of MAdCAM-1 because of the electrostatic repulsion between negative charges in the extracellular microenvironment and mucin-like region, facilitating  $\alpha$ 4 $\beta$ 7-mediated cell adhesion (Yuan et al. 2020).

A previous study revealed that different chemokines could activate integrin  $\alpha$ 4 $\beta$ 7 in a ligand-specific manner to mediate selective homing of lymphocytes to the gut via its interaction with MAdCAM-1 or to PLNs through binding with VCAM-1 (Sun et al. 2014). In particular, chemokine (C-C motif) ligand 25 (CCL25) enhances the  $\alpha$ 4 $\beta$ 7-mediated lymphocyte adhesion to MAdCAM-1 but suppresses adhesion to VCAM-1, whereas C-X-C motif chemokine 10 (CXCL10) stimulation has the opposite effect. The selective adhesion of  $\alpha$ 4 $\beta$ 7 to MAdCAM-1 and VCAM-1 is determined by the distinct active integrin conformation induced by CCL25 and CXCL10 (Sun et al. 2014; Wang et al. 2018).

### 3.3 *FN*

FN is a high-molecular-weight glycoprotein synthesized by hepatocytes and mesenchymal cells (White and Muro 2011).  $\alpha$ 4 integrins serve as alternative FN receptors in addition to the FN receptor integrin  $\alpha$ 5 $\beta$ 1 (Guan and Hynes 1990; Wayner et al. 1989a). Interestingly, the  $\alpha$ 4 integrins and  $\alpha$ 5 $\beta$ 1 recognize independent sites in intact FN. Integrin  $\alpha$ 5 $\beta$ 1 recognizes the Arg-Gly-Asp (RGD) containing cell adhesion domain in FN (Pytela et al. 1985), whereas integrin  $\alpha$ 4 $\beta$ 1 recognizes a carboxy-terminal cell adhesion region containing the Heparin II and Type III connecting-segment-1 (CS-1) domains (Guan and Hynes 1990). An acidic motif in CS-1, termed "LDV", is functionally related to RGD and responsible for  $\alpha$ 4 $\beta$ 1 binding. Integrin  $\alpha$ 4 $\beta$ 7 not only recognizes the same site within the alternatively spliced connecting segment of FN as  $\alpha$ 4 $\beta$ 1 (Ruegg et al. 1992) but also directly binds to FN splice variants containing type III repeats III5 (containing a KLDAPT

sequence) and the Extra Domain A (EDA domain, containing an EDGIHEL sequence only in cellular FN) (Pankov and Yamada 2002).

### 3.4 *Gp120*

Gp120 is an envelope glycoprotein of HIV-1. Some studies have shown the interaction between integrin  $\alpha 4\beta 7$  and gp120 through a conserved tripeptide Leu-Asp-Val/Ile (LDV/I) motif in the V2 loop of gp120 (Peachman et al. 2015; Wang et al. 2021). By mimicking the binding epitopes in MAdCAM-1, gp120 binds to  $\alpha 4\beta 7$ , which facilitates productive HIV-1 infection of  $\alpha 4\beta 7$ -expressing CD4<sup>+</sup> T cells in GALT (Cicala et al. 2009). However, unlike MAdCAM-1, which can adhere to both inactive and active  $\alpha 4\beta 7$ , gp120 predominantly binds to  $\alpha 4\beta 7$  active conformers with a highly extended conformation (Wang et al. 2021).

### 3.5 *Osteopontin*

Osteopontin is a secreted highly acidic glycoprotein originally isolated from bone. Its expression is upregulated at sites of cardiovascular injury, and monocytes and macrophages also synthesized it within injury sites (Bayless et al. 1998). As a ligand for integrin  $\alpha 4\beta 1$ , osteopontin can promote  $\alpha 4\beta 1$ -mediated leukocyte adhesion (Bayless et al. 1998). The N-terminal thrombin fragment of osteopontin has been demonstrated to bind to integrin  $\alpha 4\beta 1$  (Bayless and Davis 2001).

### 3.6 *Invasin*

Another  $\alpha 4\beta 1$  ligand is invasin, an outer membrane bacterial protein mediating the attachment of *Yersinia pseudotuberculosis* to human cells. The  $\alpha 4\beta 1$  on T cells binds strongly to purified invasin, facilitating a T-cell proliferative response (Ennis et al. 1993). Direct interactions of T cells with bacterial pathogens such as *Yersinia* may be relevant to host immune responses to bacterial infection (Ennis et al. 1993).

### 3.7 *Other $\alpha 4$ Extracellular Domain-Binding Proteins*

Several membranal proteins have been demonstrated to interact with integrin  $\alpha 4\beta 1$ , including junctional adhesion molecule-2 (JAM2), A Disintegrin and Metalloproteinase (ADAMs), CD14, and even the  $\alpha 4$  subunit itself. The binding of integrin  $\alpha 4\beta 1$  to JAM2 is only enabled following prior adhesion of JAM2 with



JAM3 and is not detectable in cells where JAM3 expression is absent (Cunningham et al. 2002). The disintegrin domains of ADAM7 and ADAM28 are recognized by  $\alpha$ 4 $\beta$ 1 and  $\alpha$ 4 $\beta$ 7, respectively, and the recognition requires integrin activation (Bridges et al. 2005). The lipopolysaccharide (LPS) receptor, CD14, a GPI-linked cell-surface glycoprotein, is a novel ligand for  $\alpha$ 4 $\beta$ 1, exhibiting similar activation-state dependent binding characteristics (Humphries and Humphries 2007). Additionally, the  $\alpha$ 4 subunit itself can serve as a ligand. There are three conserved LDV motifs in the extracellular sequence of the  $\alpha$ 4 subunit.  $\alpha$ 4 $\beta$ 1 and  $\alpha$ 4 $\beta$ 7 exhibited homophilic interactions with  $\alpha$ 4 subunits in vitro, suggesting that  $\alpha$ 4 integrins may bind to  $\alpha$ 4 subunits on adjacent cells (Altevogt et al. 1995).

## 4 Intracellular Adaptor Proteins for $\alpha$ 4 Integrins

### 4.1 $\beta$ 1 and $\beta$ 7 Cytoplasmic Tail-Binding Proteins

#### 4.1.1 Talin

Talin is a 250 kDa cytoskeletal protein that links integrins and the actin cytoskeleton. Talin comprises a 220 kDa rod domain and a 50 kDa N-terminal head domain (THD). THD harbors four subdomains, including the FERM (Band 4.1, ezrin, radixin, moesin) domain made up of F1, F2, and F3 domains, and the N-terminal F0 domain preceding the FERM domain (Calderwood et al. 1999; Critchley 2009). The F3 subdomain binds to integrin  $\beta$  cytoplasmic tails through its canonical PTB domain.  $\beta$ 1 and  $\beta$ 7 tails bind to talin via their membrane-proximal NPxY motifs (NPIY motif for  $\beta$ 1 and NPLY motif for  $\beta$ 7), and the  $\alpha$ -helical region lying between the membrane and the NPxY motif (Anthis et al. 2009; Wegener et al. 2007). The binding of talin to the  $\beta$  cytoplasmic domain requires the dephosphorylation of the Tyr in the NPxY motif and is critical for  $\alpha$ 4 integrin activation (Calderwood et al. 2002). Upon talin binding, integrin  $\beta$  cytoplasmic tails form a stable span between the TMD and cytoplasmic membrane-proximal region, which disrupts the salt bridge between the  $\alpha/\beta$  cytoplasmic tails by forming a non-covalent interaction with a conserved aspartate or glutamate residue at the  $\beta$  subunit membrane-proximal region, and consequently, activates integrin (Calderwood et al. 2013a).

#### 4.1.2 Kindlin

Kindlins also contain the conserved FERM domain and bind to a serine/threonine motif and membrane-distal NxxY motifs (Harburger et al. 2009; Malinin et al. 2010; Sun et al. 2014). In mammals, there are three kinds of kindlins (Lu et al. 2016a; Sun et al. 2014; Sun et al. 2019). Kindlin-1 is mainly expressed in epithelial cells. Kindlin-2 is expressed ubiquitously, except for the hematopoietic system. Kindlin-3 is restricted to hematopoietic cells. Kindlin and talin are indispensable for integrin

activation through their crucial functions in connecting surface-expressing integrins with intracellular actomyosin and regulating actin dynamics (Sun et al. 2019).

### 4.1.3 Filamin

Filamin, a high-molecular-weight actin-cross-linking protein, serves as an important integrin inactivator via interaction with the  $\beta$  subunit membrane-proximal NPxY motif and the subsequent serine/threonine-rich region, which overlaps the talin and kindlin-binding sequences and competes for their association with  $\beta$  tails, thereby inhibiting integrin activation (Calderwood et al. 2001).

## 4.2 $\alpha 4$ Cytoplasmic Tail-Binding Proteins

### 4.2.1 SHARPIN

SHARPIN was described as an important inactivator of integrins 10 years ago (Rantala et al. 2011). SHARPIN binds to the  $\alpha$  integrin membrane-proximal region that contains the conserved GFFKR motif. SHARPIN binding does not involve the arginine residue in the GFFKR; therefore, it does not interfere with the formation of the clasping salt bridge. Furthermore, SHARPIN bound to the  $\alpha$  tail inhibits talin and kindlin binding to the  $\beta$  tail presumably through steric hindrance (Rantala et al. 2011). Therefore, SHARPIN inhibits the activation of both integrin  $\alpha 4\beta 1$  and  $\alpha 4\beta 7$ . Moreover, SHARPIN deficiency has been shown to enhance integrin-mediated cell adhesion and reduce cell migration velocity (Park et al. 2015; Pouwels et al. 2013).

### 4.2.2 MDGI

Similar to SHARPIN, MDGI also binds directly to the cytoplasmic tail of integrin  $\alpha$  subunits, including  $\alpha 4$ , through a conserved GFFKR sequence. MDGI bound to  $\alpha$  tails retains integrin in an inactive conformation attenuating integrin-mediated adhesion, migration, and invasion (Nevo et al. 2010).

### 4.2.3 Paxillin

Paxillin is the first identified and extensively studied signaling adaptor protein of  $\alpha 4$  integrins (Liu et al. 1999). It is widely expressed and comprises five leucine-rich LD motifs in its N-terminus and four LIM domains in its C-terminus (Rose 2006). Paxillin physically associates with  $\alpha 4$  integrins, and this association markedly reduces cell spreading, focal adhesions, and stress fiber formation (Liu et al. 1999). A region of nine amino acid residues (Glu983-Tyr991) within the  $\alpha 4$

cytoplasmic domain contains a minimal sequence sufficient for paxillin binding. Furthermore, Tyr991 and Glu983 are critical residues, and either a Y991A or E983A substitution disrupts the interaction of  $\alpha$ 4 integrins with paxillin (Liu and Ginsberg 2000; Liu et al. 1999). In turn, the stretch of amino acid residues Ala176-Asp275 in the LD3 and LD4 repeats of paxillin is sufficient for binding to the  $\alpha$ 4 tail (Liu et al. 2002). The interactions between LD3 and LD4 of paxillin and the  $\alpha$ 4 tail have been confirmed by nuclear magnetic resonance (NMR) studies and the docked structures of the  $\alpha$ 4 tail with these LD repeats, suggesting possible polar and/or salt bridge and non-polar packing interactions (Chua et al. 2013). Paxillin binding to the  $\alpha$ 4 tail is also regulated by post-translational modification of the latter. Phosphorylation at Ser988 blocks paxillin binding to the  $\alpha$ 4 tail and reverses the inhibitory effect of  $\alpha$ 4 on cell spreading (Han et al. 2001). Phosphorylation of  $\alpha$ 4 is restricted to the leading edge and is absent from the sides and rear of migrating cells (Goldfinger et al. 2003). The binding of paxillin to the  $\alpha$ 4 integrin subunit in the trailing edge inhibits adhesion-dependent lamellipodium formation by blocking Rac activation (Nishiya et al. 2005).

Transgenic mice homozygous for  $\alpha$ 4 Y991A have reduced Peyer's patches and impaired mononuclear leukocyte recruitment to sites of inflammation (Feral et al. 2006). A small molecule that inhibits the interaction of paxillin and  $\alpha$ 4 integrin inhibits the accumulation of mononuclear leukocytes at sites of inflammation, proving inhibition of  $\alpha$ 4 integrin signaling as a target for the pharmacological reduction of inflammation (Kummer et al. 2010).

#### 4.2.4 Hsp90

Heat shock proteins (Hsps) are a family of proteins that display enhanced expression in response to thermal stress (Schlesinger 1990). Febrile temperatures (38.5 °C) can efficiently enhance the expression of Hsp90 in T cells and increase  $\alpha$ 4 integrin-mediated T-cell adhesion and transmigration (Lin et al. 2021; Lin and Chen 2019; Lin et al. 2019). Hsp90 binds to the ENRRDSWSY motif of the  $\alpha$ 4 cytoplasmic tail and induces association of talin and kindlin-3 with integrin  $\beta$  tails, triggering  $\alpha$ 4 integrin activation via inside-out signaling. Moreover, the N- and C-terminus of one Hsp90 molecule can simultaneously bind to two  $\alpha$ 4 tails, resulting in dimerization and clustering of  $\alpha$ 4 integrins on the plasma membrane and subsequent activation of the FAK-RhoA signaling pathway in T lymphocytes, thereby promoting T lymphocyte adhesion and transmigration. This regulation of  $\alpha$ 4 integrin function does not require the ATPase activity of Hsp90, suggesting that this function is distinct from the chaperone function of Hsp90, which requires the energy released from ATP hydrolysis (Lin et al. 2019). Abolishing Hsp90- $\alpha$ 4 interaction in vivo inhibits whole-body hyperthermia (WBH)-induced T-cell trafficking to draining lymph nodes. Moreover, in a *Salmonella typhimurium* infection-induced mouse fever model, disruption of the Hsp90- $\alpha$ 4 interaction in the mice markedly decreased the number of infiltrated T cells and increased bacterial dissemination in the small intestine, resulting in a significantly increased death rate (Lin et al. 2019). Thus, the

fever-induced Hsp90- $\alpha$ 4 integrin axis is crucial for promoting immune cell trafficking to inflamed tissues to facilitate the clearance of bacterial infection.

Because other cellular stressors can induce Hsp90 expression, the Hsp90- $\alpha$ 4 integrin pathway may also play a role in pathological conditions in allergies, autoimmune diseases, and even cancer. Whether this pathway can be targeted therapeutically to enhance or temper immune trafficking awaits further study (Bird 2019). This pathway might be exploited to make T cells “super-homers” by raising Hsp90 levels in efforts to combat cancer during the administration of cancer immunotherapy (Hampton 2019).

## 5 Activation of $\alpha$ 4 Integrins

### 5.1 Affinity Regulation

Integrin activation is accompanied by bidirectional signal transduction across the plasma membrane. Both “inside-out” and “outside-in” integrin signaling play important roles in integrin-mediated biological processes. When a cell receives an extracellular stimulus through its cell-surface receptors, such as chemokine receptors or T-cell receptor tyrosine kinases (RTKs), the transduced signals will promote the binding of intracellular integrin activators including talin and kindlins to the integrin  $\beta$  tail, leading to an integrin global conformational change into the active state with enhanced adhesiveness for extracellular ligands. This integrin activation process is termed “inside-out” activation (Kim et al. 2003; Shattil et al. 2010). In addition, integrin can also serve as a classical cell-surface signaling receptor, which transmits signals into cells upon association with its ligands via “outside-in” signaling, thereby mediating cell proliferation, survival, and differentiation (Takagi et al. 2002).

Both of these events lead to integrin affinity regulation along with striking conformational changes in the integrin molecule (Beglova et al. 2002; Luo et al. 2007; Takagi et al. 2001; Takagi et al. 2002).  $\alpha$ 4 integrins consist of a globular ligand-binding head domain involving an  $\alpha$  and  $\beta$  subunit interface localized within the  $\alpha$ 4- $\beta$  propeller and  $\beta$ 1/ $\beta$ 7- $\beta$ I domains, two long legs connected to the TMD and the cytoplasmic tail of each subunit (Yu et al. 2012). It behaves in at least three overall conformational states, including the bent conformation low-affinity state, the extended conformation with a closed or intermediate headpiece intermediate affinity state, and the extended conformation with an open headpiece high-affinity state (Fig. 1b) (Carman and Springer 2003; Luo et al. 2007).

The activation of  $\alpha$ 4 integrins is associated with an integrin molecule extension coupled with a  $\beta$  subunit hybrid domain swing-out and separation of the  $\alpha/\beta$  leg domains (Fig. 1b) (Chigaev et al. 2009; Takagi et al. 2002). Separation of the  $\alpha/\beta$  subunit transmembrane domains and cytoplasmic tails has been defined as the crucial initiator of the inside-out signaling cascade, which has been widely verified using fluorescence resonance energy transfer (FRET)-based studies (Kim et al. 2003; Wang et al. 2018). A  $\sim 62^\circ$  hybrid domain swing-out with respect to the  $\beta$ I domain is

thought to drive the downward movement of the  $\alpha$ 7 helix within the I domain and shift the ligand-binding MIDAS site into the open conformation, thereby facilitating high ligand-binding affinity (Liu et al. 2014; Wang et al. 2018; Xiao et al. 2004). This high-affinity integrin conformation can exist independently of ligand binding (Carman and Springer 2003). In the presence of its binding ligand, integrin rearranges its headpiece conformation to an open orientation with an  $\sim 80^\circ$   $\beta$  subunit hybrid domain swing-out (Takagi et al. 2002; Takagi et al. 2003), followed by conformational changes in the tailpiece, which lead to “outside-in” signal transduction.

It is noteworthy that  $\alpha$ 4 $\beta$ 7 can be activated into distinct intermediate- and high-affinity states, which exhibit selective ligand-binding preferences for MAdCAM-1 and VCAM-1 (Sun et al. 2014; Wang et al. 2018). Chemokines CCL25 and CXCL10 can stabilize the  $\alpha$ 4 $\beta$ 7 integrin in two intermediate open conformations via triggering the p38 $\alpha$  MAPK/PKC $\alpha$  and c-Src/Syk pathways, respectively, leading to different phosphorylation states of the  $\beta$ 7 tail and distinct talin and kindlin-3 binding patterns. The two intermediate open conformers of  $\alpha$ 4 $\beta$ 7 show selective adhesion to either MAdCAM-1 or VCAM-1, which results in selective homing of lymphocytes to distinct tissues in mice.

## 5.2 Avidity Regulation

Cells treated with a certain stimulus represent an obvious adhesive phenotype to the ligand-coated surface while no high-affinity soluble ligand binding is observed (Stewart et al. 1998; van Kooyk and Figdor 2000), suggesting that another regulatory pathway than “affinity regulation” contributes to integrin activation. Indeed, an integrin binding to its ligands not only changes its global conformation but also leads to clustering or patching of integrin-receptor complexes on the cell surface where cell–cell or cell–matrix contact exists, which is termed “avidity regulation” or “valency regulation” (Carman and Springer 2003; Schurpf and Springer 2011). Diverse patterns of  $\alpha$ 4 integrins clustering on living cells have been reported (Carman and Springer 2003; Shamri et al. 2002; Sun et al. 2014; Zhang et al. 2013) and can be classified into two types based on the presence of extrinsic ligands or not. In the absence of ligands, integrins redistribute to form active clusters via intrinsic signals and are transported to the cell–matrix contact surface or cell leading edge, facilitating cell adhesion and migration (Sun et al. 2014; Wang et al. 2021; Zhang et al. 2013). The cytoplasmic tail of  $\alpha$ 4 integrins makes strong positive contributions to integrin-mediated cell adhesion by upregulating integrin clustering and increasing the overall avidity of integrins (Yauch et al. 1997). Hsp90 has recently been identified as a novel  $\alpha$ 4 intracellular binding protein (Lin et al. 2019). The N-terminal domain (NTD) and C-terminal domain (CTD) of Hsp90 can directly bind to the  $\alpha$ 4 tail. Thus, one Hsp90 molecule simultaneously associates with two  $\alpha$ 4 subunits, which induces  $\alpha$ 4 integrin dimerization and clustering on the cell membrane and subsequent activation of integrin downstream signaling.

Redistribution of  $\alpha 4$  integrins on the cell surface also occurs in a ligand-dependent manner. This is probably caused by the multivalent property of integrin-binding ligands, such as FN.

## 6 Expression and Physiological Functions of $\alpha 4$ Integrins

### 6.1 Expression of Integrin $\alpha 4\beta 1$ and $\alpha 4\beta 7$

Integrin  $\alpha 4\beta 1$  is constitutively expressed on most leukocytes (Luster et al. 2005). In general, neutrophils are assumed not to express  $\alpha 4$  integrins. However,  $\alpha 4$  integrins have been demonstrated to play a role in mediating neutrophil adhesion and migration (Johnston and Kubes 1999), suggesting that low levels of  $\alpha 4$  integrins on neutrophils suffice for functional activity. Moreover,  $\alpha 4\beta 1$  expression occurs in hematopoietic stem cells (HSCs) (Williams et al. 1991) and non-hematopoietic cells in multiple embryonic tissues, including somites, heart, vascular smooth muscle and skeletal muscle, the neuroepithelium of the embryonic retina, and neural crest-derived cells, such as melanoblasts (Sheppard et al. 1994; Stepp et al. 1994; Yang et al. 1995).  $\alpha 4\beta 1$  is also expressed in various tumor cells, including metastatic melanoma and gastric cancer cells (Mould et al. 1994; Park et al. 2004; Rebhun et al. 2010), indicating vital roles in both physiological and pathological processes.

The expression of integrin  $\alpha 4\beta 7$  is restricted on hematopoietic cells. A group of immune cells has been reported to express integrin  $\alpha 4\beta 7$  constitutively, including lymphocytes, NK cells, mast cells, basophils, eosinophils, macrophages, and monocytes (von Andrian and Mackay 2000). Under a steady-state, naïve lymphocytes exhibit a relatively low expression level of integrin  $\alpha 4\beta 7$  (Erle et al. 1994). Among them, most B lymphocytes show relatively high expression of integrin  $\alpha 4\beta 7$  compared with most T lymphocytes in the peripheral lymphoid organs, including the spleen, Peyer's patches, and lymph nodes (Andrew et al. 1996). Intestinal dendritic cells (DCs)-derived retinoic acid (RA) has been shown to upregulate  $\alpha 4\beta 7$  expression on memory or activated gut-tropic lymphocytes, promoting lymphocyte homing to mucosal tissues or GALT effectively during intestinal immune responses (Hao et al. 2021; Iwata et al. 2004; Mora et al. 2006). In contrast, the majority of naïve or memory T cells, which lack  $\alpha 4\beta 7$  expression in circulation, express  $\alpha 4\beta 1$  instead (DeNucci et al. 2010). These cells prefer to home to non-mucosal tissues via binding to VCAM-1 (Rott et al. 1996; Rott et al. 1997). Interleukin-7 (IL-7) can potently induce  $\alpha 4\beta 7$  expression on naïve T cells and is closely related to  $\alpha 4\beta 7$  activation, resulting in intestinal homing of lymphocytes and immunologic reconstitution in lymphopenic hosts (Cimbro et al. 2012). As observed in hypereosinophilic patients, eosinophils characterized with high  $\alpha 4\beta 7$  expression exhibit preferential gut homing rather than trafficking to the lungs (Brandt et al. 2006). Moreover, integrin  $\alpha 4\beta 7$  is significantly upregulated on both peripheral naïve and memory T-cell subsets in intestinal graft-versus-host disease (GvHD) patients (Chen et al. 2009; Chen et al.

2013), suggesting integrin  $\alpha 4\beta 7$  serves as a crucial regulator in both homeostatic and pathologic conditions.

## 6.2 *Integrin $\alpha 4\beta 1$ and $\alpha 4\beta 7$ in Leukocyte Homing*

The recruitment of leukocytes from blood circulation to lymphoid organs and inflamed tissues is regulated by the sequential interactions of adhesion and signaling molecules on leukocytes and blood vessels, essential to immune surveillance and host defense (Butcher and Picker 1996). This recruitment process consists of a highly ordered adhesion cascade that includes tethering and rolling leukocytes along vessel walls of HEVs, chemokine-induced activation, firm arrest, and transendothelial migration (von Andrian and Mempel 2003). The initial transient contact of the circulating leukocytes with the vascular endothelium leads to leukocytes rolling along the vascular wall with greatly reduced velocity. The interaction mainly mediates this process between selectins and their ligands. In addition, inactive  $\alpha 4\beta 1$  and  $\alpha 4\beta 7$  integrins are also able to support lymphocyte rolling via binding to their endothelial ligands, VCAM-1 and MAdCAM-1 (Ley et al. 2007), respectively. After chemokine-induced activation of lymphocytes on the endothelium,  $\alpha 4$  and  $\beta 2$  integrins are activated to mediate cell arrest. During this process, chemokines activate integrins through the rapid triggering of the signaling network that regulates the binding of intracellular effector proteins (e.g., talin or kindlin) to the cytoplasmic domains of integrins, which induces integrin activation (Hogg et al. 2011). The final transmigration step across HEVs involves multiple adhesion molecules, including  $\alpha 4\beta 1$ ,  $\alpha L\beta 2$ , VCAM-1, intercellular adhesion molecule-1 (ICAM-1), ICAM-2, platelet endothelial cell adhesion molecule-1 (PECAM-1), junctional adhesion molecule-1 (JAM-1), and JAM-2 (Carman and Springer 2004). Notably,  $\alpha 4$  integrins are involved in each step of leukocyte homing, and thus, have essential roles in regulating lymphocyte trafficking to lymphoid organs and inflamed tissues (Lin et al. 2019).

## 6.3 *Integrin $\alpha 4\beta 7$ in Lymphocyte Gut-Tropic Trafficking and GALT Formation*

Integrin  $\alpha 4\beta 7$  is the most important gut-homing adhesion molecule in targeting lymphocytes trafficking to mucosal lymphoid tissues, such as Peyer's patches and mesenteric lymph nodes (MLNs) (Habtezion et al. 2016). Naïve and central memory lymphocytes in circulation are recruited to enter the mucosal lymphoid tissues via interaction between surface-expressing  $\alpha 4\beta 7$  and its ligand MAdCAM-1 expressed on the HEVs localized in these tissues (Laudanna et al. 2002). Along with priming in the GALT, gut-homing lymphocytes undergo  $\alpha 4\beta 7$  and CCR9 upregulation by RA

produced by DCs and/or stromal cells in the MLN, which imprints them with gut tropism and directs these cells to the LP of the small intestine (Agace 2010; Agace and Persson 2012). The conventional intraepithelial lymphocytes (IELs) derived from circulating T cells work similarly as LP lymphocytes (LPLs) (Habtezion et al. 2016), whereas the unconventional IELs originate from CD8<sup>+</sup> thymocytes, which already express  $\alpha 4\beta 7$  and CCR9 in the thymus, bypassing the imprinting process in GALT (Guy-Grand et al. 2013; Staton et al. 2006).

Integrin  $\alpha 4\beta 7$  deficiency shows no defect in T and B cell development in mice, suggesting it is not required for lymphocyte development. However, in  $\beta 7^{-/-}$  mice, the failure of  $\alpha 4\beta 7$ -induced lymphocyte homing results in a large reduction in gut-tropic lymphocytes within the intestinal tissue, which eventually leads to abnormal development of GALT (Wagner et al. 1996). In addition, an integrin  $\alpha 4\beta 7$  mutation, which fails to transmit talin-induced TMD topology and blocks lymphocyte gut homing, results in GALT development disruption (Sun et al. 2018). These data suggest a vital role of  $\alpha 4\beta 7$  in the development of GALT architecture.

#### **6.4 Role of Integrin $\alpha 4\beta 7$ in Innate Immune Cells**

Integrin  $\alpha 4\beta 7$  has also been reported to regulate innate immune cell tolerogenic functions in the mucosal immune system beyond lymphocyte trafficking (Kempster and Kaser 2014; Villablanca et al. 2014). A subset of  $\alpha 4\beta 7$ -expressing Lin<sup>neg</sup>Ly6C<sup>low</sup> BM cell progenitors give rise to RA-producing DCs, which are required to imprint gut-homing T cells. Moreover, integrin  $\alpha 4\beta 7$  is indispensable for the localization and reconstitution of these tolerogenic gut mononuclear phagocytes with the ability to induce Foxp3<sup>+</sup> regulatory T cells and IL-10-producing T cells (Villablanca et al. 2014).

#### **6.5 Integrin $\alpha 4\beta 1$ in T-Cell Proliferation, Activation, and Survival**

Integrin  $\alpha 4\beta 1$  can influence T cells in different ways. Anti-CD3 plus the integrin  $\alpha 4\beta 1$  ligand (CS1) can induce significant proliferation of CD4<sup>+</sup> cells (Engelhardt et al. 1998; Nojima et al. 1990). Certain antibodies against integrin  $\alpha 4\beta 1$  block the effector activity of class I- and II-specific cytotoxic T lymphocytes (CTLs) in vitro (Clayberger et al. 1987; Takada et al. 1989). Integrin  $\alpha 4\beta 1$  also plays a regulatory role for T lymphocyte-antigen presenting cell cognate immune interactions by concentrating at the peripheral supramolecular activation complex (pSMAC) of the immune synapse and driving Th1 responses (Mittelbrunn et al. 2004). Furthermore, adhesion mediated by  $\alpha 4\beta 1$ -VCAM-1 interaction promotes both T and B cell



survival. Blockade of the interaction via monoclonal antibodies (mAbs) causes increased cell apoptosis (Koopman et al. 1994; Leussink et al. 2002).

## **6.6 *Integrin $\alpha$ 4 $\beta$ 1 in Hematopoietic Stem Cell Maintenance and Hematopoiesis***

Integrin  $\alpha$ 4 $\beta$ 1 also plays an important role in developing and maintaining HSCs and hematopoiesis. Disturbing progenitor cell interaction with stromal cells by blocking  $\alpha$ 4 integrin inhibits lymphopoiesis in vitro (Miyake et al. 1991). Analyzing hematopoiesis in integrin  $\alpha$ 4- and  $\beta$ 1-deficient somatic chimeric mice demonstrated a requirement of  $\alpha$ 4 $\beta$ 1 in HSC homing to the fetal liver (Arroyo et al. 1999).  $\alpha$ 4 integrins are also required for hematopoietic precursor cell interactions with BM stromal cells and act as a retention signal for hematopoietic progenitors to remain in the BM compartment (Arroyo et al. 1996). Lack of  $\alpha$ 4 integrins leads to premature detachment of hematopoietic progenitors and low yields of mature cells in peripheral tissues (Arroyo et al. 1999). It is noteworthy that all detected requirements for  $\alpha$ 4 integrins in hematopoiesis result from  $\alpha$ 4-deficient mice. However, the lack of  $\alpha$ 4 integrins solely on hematopoietic cells in the adult does not hamper hematopoiesis, suggesting  $\alpha$ 4 integrins in non-hematopoietic cells may involve hematopoiesis (Brakebusch et al. 2002; Bungartz et al. 2006; Scott et al. 2003).

## **6.7 *Integrin $\alpha$ 4 $\beta$ 1 and Embryonic Development***

$\alpha$ 4 $\beta$ 1 is crucial in embryonic development. Deficiency of the  $\alpha$ 4 integrin subunit leads to embryonic lethality because of a failure in cell–cell adhesion events in placental and cardiac development (Yang et al. 1995). The early defect in  $\alpha$ 4-null embryos is characterized by a failure of the allantois to fuse with the chorion during placental development, and these embryos die by approximately embryonic day 11 (Yang et al. 1995). Although in a few cases, the fusion of the allantois and the chorion is successful, those embryos still die at approximately embryonic day 11.5 because of severe hemorrhage in the heart region caused by a failure in the epicardium-myocardium attachment during cardiac development (Yang et al. 1995). As a major counter-receptor of the  $\alpha$ 4 $\beta$ 1 integrin, VCAM-1-deficient embryos show the same placental and cardiac defects, suggesting that these defects are probably caused by  $\alpha$ 4 $\beta$ 1/VCAM-1-mediated adhesive interactions during embryonic development (Gurtner et al. 1995; Kwee et al. 1995). Whether  $\alpha$ 4 $\beta$ 1 and VCAM-1 are involved in skeletal muscle development is controversial (Rosen et al. 1992; Yang et al. 1996).

## 7 $\alpha 4$ Integrins in Disease

### 7.1 $\alpha 4$ Integrins in Cancer

Altered integrin expression and function have been comprehensively reported in many types of human cancer and are tightly correlated with different stages of tumor progression, patient responses to antineoplastic therapy, and survival rates of patients with cancer (Table 1) (Hamidi and Ivaska 2019). Integrin  $\alpha 4\beta 1$  has been

**Table 1**  $\alpha 4$  integrin-related diseases

Disease	Integrin	Function of integrins and the targeting drugs	References
Neuroblastoma	$\alpha 4\beta 1$	PIH4 (targeting the $\alpha 4$ subunit) blocks neuroblastoma metastasis.	Gazitt and Akay (2004), Young et al. (2015)
Multiple myeloma (MM)	$\alpha 4\beta 7$	MMG49 (targeting highly-activated integrin $\beta 7$ )-derived chimeric antigen receptor (CAR)-T cells significantly dampen MM progression.	Hosen (2020), Hosen et al. (2017)
Thymic lymphoma	$\alpha 4\beta 7$	Integrin $\alpha 4\beta 7$ is involved in abnormal lymphocyte trafficking to the hyperplastic thymus, leading to thymic lymphoma development.	Michie et al. (1995)
Colorectal cancer (CRC)	$\alpha 4\beta 7$	$\alpha 4\beta 7$ mediates the recruitment of IFN- $\gamma$ -producing CD4 <sup>+</sup> T cells, cytotoxic CD8 <sup>+</sup> T cells, and NK cells to the CRC tissue where they exert effective anti-tumor immune responses.	West et al. (2015), Zhang et al. (2021)
Inflammatory bowel disease (IBD)	$\alpha 4\beta 7$	Natalizumab (targeting the $\alpha 4$ subunit); Vedolizumab (targeting the $\alpha 4\beta 7$ heterodimer); Abruilumab (AMG-181, targeting the $\alpha 4\beta 7$ heterodimer); Etrolizumab (targeting the $\beta 7$ subunit).	Mezu-Ndubuisi and Maheshwari (2021), Sandborn et al. (2013), Pan et al. (2013) Selinger et al. (2018)
Multiple sclerosis (MS)	$\alpha 4\beta 1$	Natalizumab can reduce the risk of the sustained progression of disability and the rate of clinical relapse in patients with relapsing MS.	Polman et al. (2006), Radue et al. (2010), Rudick et al. (2006)
Acquired immunodeficiency syndrome (AIDS)	$\alpha 4\beta 7$	Vedolizumab and etrolizumab have shown efficient inhibition of gp120 binding to $\alpha 4\beta 7$ .	Wang et al. (2021), Burnie and Guzzo (2019), Sneller et al. (2019)
Graft-versus-host disease (GvHD)	$\alpha 4\beta 7$	Vedolizumab has now been evaluated to treat steroid-refractory (SR) GI aGvHD.	Chen et al. (2019), Danylesko et al. (2019)

detected on both benign and malignant cells of the melanocytic lineage and suppresses metastasis formation in some experimental tumor models (Gazitt and Akay 2004). However, in the MYCN<sup>low</sup> neuroblastoma, integrin  $\alpha 4$  expression enhances experimental metastasis in a syngeneic tumor model, reconstituting a pattern of organ involvement similar to that seen in patients. Accordingly, antagonism of  $\alpha 4\beta 1$  (PIH4, antibody against integrins  $\alpha 4$ ) blocks metastasis, suggesting the adhesive function of  $\alpha 4\beta 1$  is required during neuroblastoma metastasis (Young et al. 2015).

A previous study documented the crucial role of integrin  $\alpha 4\beta 7$  in the pathogenesis and development of multiple myeloma (MM), also called Kahler's disease, a blood cancer that forms from the abnormal aggregation of antibody-producing plasma cells (Hosen 2020). In MM patients, cancerous plasma cells preferentially accumulate in the BM microenvironment, which crowds out healthy leukocytes and generates superfluous invalid immunoglobulins into blood circulation and bones, thereby causing severe complications. MM cells selectively adhere to either the BM microenvironment ECM components or multiple cell types residing in the BM, including hematopoietic cells, stromal cells, endothelial cells, and osteocytes, through interactions between adhesion molecules, such as integrins  $\alpha 4\beta 1$ ,  $\alpha 4\beta 7$ ,  $\alpha L\beta 2$ , and their ligands VCAM-1, FN, and ICAM-1 (Shishido et al. 2014). In particular, integrin  $\alpha 4\beta 7$  is a central mediator in orchestrating MM cell adhesion, migration, aggregation, and extraversion during cancer progression (Neri et al. 2011). The expression of integrin  $\beta 7$  subunit could be upregulated by overexpression of *c-maf* gene (Hurt et al. 2004). The upregulated expression of integrin  $\beta 7$  in MM is inversely correlated with patient survival outcomes (Neri et al. 2011). Depletion of  $\beta 7$  expression in MM cells impairs the adhesion between cancer cells and ECM ligands, such as FN. It weakens its transwell migration induced by the BM-homing chemokine, CXCL12 (stromal cell-derived factor-1, SDF-1), reducing MM cells assembling in the BM microenvironment and subsequently alleviating cancer progression in the mouse model (Hosen 2020; Neri et al. 2011). Moreover, the integrin  $\beta 7$  subunit is primarily associated with the  $\alpha 4$  subunit on MM cells rather than the  $\alpha E$  subunit (Hosen et al. 2017), underlining the dominating effects of  $\alpha 4\beta 7$  in regulating MM pathogenesis. It is noteworthy that integrin  $\beta 7$  on MM cells has been unexpectedly detected to adopt a constitutively active conformation in the process of MM-specific cell-surface antigen screening (Hosen 2020; Hosen et al. 2017). The MM-specific mAb MMG49, which only recognizes the highly-activated conformation of the integrin  $\beta 7$  chain, specifically targets constitutively activated  $\beta 7$  expressed on MM cells instead of other CD45<sup>+</sup> normal leukocytes in the BM. Usage of MMG49-derived chimeric antigen receptor (CAR)-T cells significantly dampens MM progression and prolongs the survival of tumor-bearing mice without damaging normal hematopoietic cells in the mouse model (Hosen et al. 2017). This suggests promising results from targeting a specific active conformer of  $\alpha 4\beta 7$  in anti-MM therapy in the future.

Integrin  $\alpha 4\beta 7$  is involved in abnormal lymphocyte trafficking to the hyperplastic thymus, characterized by an increased number of medullary blood vessels showing prominent HEV morphology and MAdCAM-1 expression, leading to thymic lymphoma development (Michie et al. 1995). Importantly, as a gut-tropic molecule,

integrin  $\alpha 4\beta 7$  plays a profound role in regulating the progression of colorectal cancer (CRC).  $\alpha 4\beta 7$  mediates the recruitment of IFN- $\gamma$ -producing CD4<sup>+</sup> T cells, cytotoxic CD8<sup>+</sup> T cells, and NK cells to the CRC tissue where they exert effective anti-tumor immune responses (West et al. 2015). A recent study showed that  $\beta 7$  expression decreased in tumor-derived compared to normal tissue-derived CD8<sup>+</sup> T cells (Zhang et al. 2021). Higher  $\beta 7$  expression levels are correlated with longer patient survival, higher cytotoxic immune cell infiltration, lower somatic copy number alterations, decreased mutation frequency of *APC* and *TP53*, and better response to immunotherapy.  $\beta 7$  deficiency led to exaggerated tumorigenesis and progression in both *Apc*<sup>min/+</sup> spontaneous and MC38 orthotopic models of CRC, which could have been caused by the reduced infiltration of activated CD8<sup>+</sup> T cells, effector memory CD8<sup>+</sup> T cells, IFN $\gamma$ <sup>+</sup> CD8<sup>+</sup> T cells, and other immune cell subsets that are essential players in anti-tumor immunity.

## 7.2 Integrin $\alpha 4\beta 1$ in Multiple Sclerosis (MS)

The integrin  $\alpha 4\beta 1$ /VCAM-1 axis plays an essential role in the homing of inflammatory leukocyte cells into the central nervous system (CNS) in different experimental autoimmune encephalomyelitis (EAE) models (Table 1) (Engelhardt et al. 1998; Kent et al. 1995a; Kerfoot and Kubes 2002; Yednock et al. 1992). Although encephalitogenic T cells express both  $\alpha 4\beta 1$  and  $\alpha 4\beta 7$  at similar levels, neutralizing  $\alpha 4\beta 7$  with antibodies does not inhibit EAE development (Engelhardt et al. 1998). It has been reported that antibodies to VCAM-1 inhibit the pathogenicity of encephalitogenic Th1 cells in vivo (Baron et al. 1993). The mouse mAb AN100226m, a potent antibody blocking  $\alpha 4$  integrin-mediated binding to FN and VCAM-1, has been demonstrated to inhibit lymphocyte adhesion to tumor necrosis factor (TNF)-stimulated brain endothelium and is shown to reverse disease progression in the EAE model (Kent et al. 1995b). The humanized antibody AN100226, natalizumab, can reduce the risk of the sustained progression of disability and the rate of clinical relapse in patients with relapsing MS (Polman et al. 2006). It is noteworthy that few patients undergoing natalizumab therapy in combination with other immunoregulatory and immunosuppressive agents were diagnosed with progressive multifocal leukoencephalopathy (PML) after its initial approval, therefore the usage of the agent is restricted to monotherapy in patients with relapsing forms of MS (Warnke et al. 2010). Furthermore, the combination of natalizumab with interferon- $\beta$  1 $\alpha$  (IFN- $\beta$  1 $\alpha$ ) is significantly more effective than IFN- $\beta$  1 $\alpha$  alone in patients with relapsing MS (Radue et al. 2010; Rudick et al. 2006). Thus, adhesion-molecule inhibitors hold promise as an effective treatment for relapsing MS.

### 7.3 *Integrin $\alpha$ 4 $\beta$ 7 in Inflammatory Bowel Disease (IBD)*

IBD is a chronic and prejudicial inflammation of the gastrointestinal (GI) tract, including Crohn's disease (CD) and ulcerative colitis (UC). The former is diagnosed with intermittent transmural inflammation that occurs mostly on the terminal ileum of the small intestine before the large intestine (colon) but can also affect other sites in the GI tract from the mouth to the anus. Unlike CD, UC primarily occurs in the large intestine (colon) and the rectum, with pathological features characterized by continuous inflammation in the superficial mucosa starting from the rectum and extending further into the large intestine (Gorfu et al. 2009). CD and UC share common clinical symptoms, including persistent diarrhea, abdominal pain, rectal bleeding, bloody stools, body weight loss, and fatigue, seriously hindering the quality of life of the patient (Waljee et al. 2009).

Activation of the immune response generally occurs in IBD patients, manifested by various alterations in inflammatory cytokines and Ig family protein production (de Souza and Fiocchi 2016). During the progression of IBD, the chronic inflammation is accompanied by the accumulation of macrophages, CD4<sup>+</sup> and CD8<sup>+</sup> T cells, B cells, and other leukocytes in the LP, and crypt abscesses with a high production of cytokines, including TNF- $\alpha$ , IFN- $\gamma$ , IL-12, IL-13, and IL-5 (de Souza and Fiocchi 2016; Strober et al. 2007; Xavier and Podolsky 2007). Of note, integrin  $\alpha$ 4 $\beta$ 7-mediated lymphocyte trafficking to intestinal tissues is deemed the most significant inducement in IBD etiopathogenesis (Table 1) (Neurath 2014; Zhang et al. 2016), whose inhibitors show promising therapeutic effects in clinical implications of IBD patients. Natalizumab, which targets the integrin  $\alpha$ 4 subunit to block  $\alpha$ 4 $\beta$ 7 binding to VCAM-1/MAdCAM-1 and  $\alpha$ 4 $\beta$ 1-VCAM-1 binding, provides favorable effects in treating CD patients who are refractory to standard therapy (Mezu-Ndubuisi and Maheshwari 2021). Unfortunately, PML, a rare and often fatal side effect of natalizumab in IBD patients, restricts the use of this drug during treatment (Li et al. 2018b). Vedolizumab, an integrin  $\alpha$ 4 $\beta$ 7 blocking mAb, came on the market for IBD treatment in 2014 from Takeda. It specifically inhibits the interaction between  $\alpha$ 4 $\beta$ 7 and MAdCAM-1 without affecting  $\alpha$ 4 $\beta$ 1 function; thus, it avoids the PML-associated side effects of natalizumab and other systemic immunosuppression influences (Sandborn et al. 2013).

The successful use of vedolizumab in IBD highlights the research and development of therapeutic targets aiming at the gut-tropic molecule  $\alpha$ 4 $\beta$ 7. Recently, abrilumab (Amgen), also called AMG-181, targeting the  $\alpha$ 4 $\beta$ 7 integrin heterodimer, shows encouraging results in a phase II study on moderate to severe CD and UC (Pan et al. 2013). In addition, etrolizumab from Genentech, mAb specifically targets the  $\beta$ 7 subunit to block both  $\alpha$ 4 $\beta$ 7- and  $\alpha$ E $\beta$ 7-mediated adhesion, is now in an ongoing robust phase II study on UC and phase III study on CD (Selinger et al. 2018).

## 7.4 *Integrin $\alpha4\beta7$ in Acquired Immunodeficiency Syndrome (AIDS)*

Acute HIV infection features high virus replication within the GALT, accompanied by a remarkable reduction in CD4<sup>+</sup> T cells, especially the gut-homing integrin  $\alpha4\beta7$ -expressing CD4<sup>+</sup> T cells (Table 1) (Cicala et al. 2009; Guadalupe et al. 2003). It has been demonstrated that the HIV-1 envelope glycoprotein gp120 can bind  $\alpha4\beta7$  through its key residues localized in the V2 domain (V2-loop) (Richardson et al. 2015), facilitating the HIV virion- $\alpha4\beta7^+$ CD4<sup>+</sup> T-cell complex recruitment to intestinal tissues via an  $\alpha4\beta7$  interaction with MAdCAM-1 (Liu and Lusso 2020). During acute HIV infection, the  $\alpha4\beta7^{\text{high}}$  memory CD4<sup>+</sup> T cells are thought to be the early and primary targets of HIV (Cicala et al. 2011; Pena-Cruz et al. 2013).

Integrin  $\alpha4\beta7$ -gp120 binding and further incorporation of  $\alpha4\beta7$  in HIV virions exist in a selective manner (Guzzo et al. 2017; Wang et al. 2021). It was recently reported that gp120 only binds to  $\alpha4\beta7$  active conformers with highly extended conformations, which can be induced by particular chemokines, such as CCL19 and CCL25, and the binding of gp120 to  $\alpha4\beta7$  induces the activation of multiple signal pathways in T cells (Wang et al. 2021). The  $\alpha4\beta7$ -directed virus gut-tropic distribution subsequently leads to HIV colonization and replication in gut-related tissues in the early stage of HIV infection, further resulting in massive depletion of CD4<sup>+</sup> T cells and structural damage of the GI tract (Brenchley et al. 2004; Cicala et al. 2009).

The  $\alpha4\beta7$  blocking mAb vedolizumab and  $\beta7$  blocking mAb etrolizumab have shown efficient inhibition of gp120 binding to  $\alpha4\beta7$  (Wang et al. 2021), supporting the inhibitory effects of  $\alpha4\beta7$  neutralization in HIV infection (Li et al. 2018a). To date, several open-label, single-arm clinical trials with vedolizumab are being conducted with HIV-infected individuals in the USA, Spain, Canada, and France to better evaluate the effects of the  $\alpha4\beta7$  inhibitor in anti-HIV therapy (Burnie and Guzzo 2019; Sneller et al. 2019).

## 7.5 *Integrin $\alpha4\beta7$ in Graft-Versus-Host Disease*

GvHD is identified as two distinct entities: acute and chronic GvHD (Martinez-Cibrian et al. 2021). Acute GvHD (aGvHD) is an immune syndrome induced by activated donor effector T cells, which are CTLs, recognizing host antigens and initiating immune responses to attack host organs, such as the GI tract, skin, and liver (Table 1) (Welniak et al. 2007). It frequently occurs in patients adopting allogeneic HSCT, whose grade of aGvHD is negatively correlated with prognosis and is considered the major cause of mortality post-HSCT surgery (Deeg 2007; Martin et al. 2012).

During aGvHD, donor T cells migrate to intestinal tissues, such as MLN and Peyer's patches utilizing the integrin  $\alpha4\beta7$ -MAdCAM-1 interaction (Dutt et al. 2007). It has been shown that depletion of  $\alpha4\beta7$  (Petrovic et al. 2004) or  $\beta7$

(Waldman et al. 2006) on donor T cells and interception of the  $\alpha 4\beta 7$ –MAdCAM-1 interaction (Ueha et al. 2007) can alleviate aGvHD-induced gut damage in murine allogeneic BM transplantation (BMT) models. Promising data obtained from murine transplant models suggests the usage of integrin  $\alpha 4\beta 7$  blocking mAb that prevents  $\alpha 4\beta 7$ –MAdCAM-1 binding in the treatment of intestinal aGvHD. Integrin  $\alpha 4\beta 7$  mAb vedolizumab has now been evaluated to treat steroid-refractory (SR) GI aGvHD in phase I trials and showed a reduced incidence of high-grade aGvHD without generating adverse effects (Chen et al. 2019; Danylesko et al. 2019). However, these results need to be further validated in prospective clinical trials.

## 8 Conclusion and Future Perspectives

Integrin  $\alpha 4\beta 1$  and  $\alpha 4\beta 7$  are constitutively expressed on some leukocyte populations. Upon stimulation,  $\alpha 4$  integrin expression can be induced on the surface of some leukocytes (Hemler et al. 1987b; Kirveskari et al. 2000). The  $\alpha 4$  integrin-mediated aberrant homing of leukocytes to the CNS or gut plays a critical role in MS or IBD, respectively. Blocking antibodies targeting  $\alpha 4$  integrins, including natalizumab and vedolizumab, have been used clinically and show efficacy in treating MS and IBD. It is noteworthy that natalizumab treatment may induce PML. Moreover, some UC patients exhibited aggravated colitis after vedolizumab, which the aberrant innate immune response may cause after fully blocking  $\alpha 4\beta 7$ . Therefore, instead of fully blocking  $\alpha 4$  integrins, more precise regulation of  $\alpha 4$  integrin function, such as blocking the aberrant integrin activation, could be a better strategy for managing MS and IBD. Screening small molecule compounds or mAbs for blocking the activation of  $\alpha 4$  integrins could lead to discovering next-generation MS/IBD drugs with fewer adverse effects (Baiula et al. 2019).

The interaction between integrins and different ligands enables the targeting of lymphocytes to different tissues. Each leukocyte integrin can recognize multiple ligands, which makes the tissue-specific leukocyte homing complicated. Some studies have revealed that different chemokines can induce ligand-specific activation of integrin  $\alpha 4\beta 7$ , which allows the selective binding of  $\alpha 4\beta 7$  to either MAdCAM-1 or VCAM-1 to ensure a tissue-specific homing of lymphocytes (Sun et al. 2014; Wang et al. 2018). Notably, when chemokines promote  $\alpha 4\beta 7$  to one ligand, it inhibits  $\alpha 4\beta 7$  binding to the other ligand. The chemokine-induced inhibition of  $\alpha 4\beta 7$  binding to its ligands may be involved in the selective recruitment of different immune cells into tissues under pathological conditions, which deserves further investigation.

Although integrin  $\alpha 4\beta 7$  has been characterized in-depth as a gut-homing molecule expressed on the surface of lymphocytes, it also plays a role in several innate immune cell subtypes, including the BM precursor cells, which differentiate into tolerogenic, RA-secreting DCs, and NK cells and monocytes (Bouchentouf et al. 2010; Picarella et al. 1997; Schleier et al. 2020; Villablanca et al. 2014). The regulatory function of  $\alpha 4\beta 7$  appears disparate among different cell types and may

be more complex than originally speculated. More precise studies need to be conducted to investigate the distinct functions in specific immune cell subsets during both homeostatic and pathologic processes.

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