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# INTEGRINS AND THEIR ROLE IN INFLAMMATORY BOWEL DISEASE: MECHANISMS AND THERAPEUTIC IMPLICATIONS

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## ABSTRACT

Inflammatory bowel disease results from an atypical immune reaction in the intestinal mucosa, leading to an enhanced release of mediators that promote inflammation like eicosanoids, platelet-activating factors, cytokines, and reactive oxygen/nitrogen metabolites. The multifactorial-driven disease, which consists of Crohn's disease and ulcerative colitis, is primarily characterized by a discrepancy between pro-inflammatory and anti-inflammatory mediators. The treatment strategy for IBD includes monoclonal antibodies targeting interleukins, TNF-α, as well as Integrin-CAM interactions. Integrins, which are heterodimers with α and β subunits, play a significant role in leukocyte trafficking to the intestinal wall during the pathogenesis of IBD. So targeted anti-integrin therapy offers a promising option in the treatment of IBD. In this review, we have detailed integrins, their activation, 'their role in the pathophysiology of IBD, and various anti-integrin medications.

**KEYWORDS:** IBD, Ulcerative colitis, Crohn's Disease, Integrins, Cell adhesion molecules (CAMs), Leukocyte trafficking.

## INTRODUCTION

Integrins, a group of cell-surface receptors found in eukaryotes, facilitate dynamic interactions between cells and the extracellular matrix (ECM), an important feature of multicellular organisms. Integrins are type I transmembrane proteins that consist of

heterodimers formed by α and β subunits. They feature large extracellular domains, a single transmembrane section, and a short cytoplasmic tail. In humans, there are 24 distinct integrin heterodimers made up of 18 α and 8 β subunits, exhibiting overlapping yet non-redundant functions. The particular pairing of α and β subunits dictates the ligand and signalling specificity.[1,2]

The ECM proteins or counter-receptors on neighbouring cells are recognized by the integrins. Glycoproteins such as von Willebrand factor, fibronectin, laminin, thrombospondin, vitronectin, collagen, osteopontin, and tenascin, are examples of ECM molecules, and Ig-superfamily cell adhesion molecules such as vascular cell-adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) that influence cell adhesion.[1,2]

The well-known amino acid order Arg-Gly-Asp (RGD), initially discovered in fibronectin, serves as a primary motif for cell recognition, which was a key finding in the identification of integrins. Subsequently, it was found that the RGD order is present in many extracellular matrix (ECM) components and that it frequently facilitated cell adhesion.[2]

## HISTORICAL OVERVIEW

Erkki Ruoslahti and Richard O. Hynes, founders of the integrin family, contributed significant data in early cell adhesion research. Integrins, evolutionary cell adhesion receptors, have only been defined at the molecular level for 25 years. Successful identification methods used antibodies blocking cell adhesion and mapping fibronectin's minimal adhesion site to the RGDS sequence.

The study focused on optimizing ion composition in purification buffers, finding that manganese ions increased integrin affinity. An antibody-based method was used in 1986 to successfully create a cDNA encoding the chick integrin β1 subunit, which evolved into the term "integrin." The crucial function of these receptors in preserving the integrity of the cytoskeletal-ECM connection.

During the 1980s, researchers explored a range of cell surface proteins, which included position-specific antigens found in Drosophila, very late activation antigens present on immune cells, cell surface receptors located on lymphoid and myeloid cells, as well as glycoproteins found on platelets. The cloning of cDNAs coding for these proteins demonstrated their connection to fibronectin receptors. These receptors were isolated through

the use of RGD peptides or antibodies that block cell adhesion, and all were identified as part of the integrin family of cell adhesion receptors.[3]

## STRUCTURE OF INTEGRIN

The extracellular α and β subunits are made up of several subdomains, featuring a rounded N-terminal head domain along with two extended C-terminal legs that link to the transmembrane and cytoplasmic domains of each subunit.[4]

### Integrin α subunit

The α subunit features a seven-bladed β-propeller connected to the thigh, calf-1, and calf-2 domains, forming a leg structure that supports the integrin head. The last third or fourth blades of the β-propeller contain EF-hand domains that bind $Ca^{2+}$ on the lower side, away from the ligand-binding surface. The allosteric influence of $Ca^{2+}$ binding at these sites is evident in its effect on ligand binding.[3]

An additional (I)-domain of about between the second and third blades of the β-propeller domain, there are 200 amino acids located in half of the alpha subunits. An I domain, or A domain, exists in nine different integrin α chains.[3]

I domain is present in number of α subunits include α1, α2, α10, α11, αL, αM, αX, αD, and αE, while non-I-domain subunits include α3, α4, α5, α6, α7, α8, α9, αV, and αIIb. This I domain present in the integrins is essential for ligand binding and cell-to-cell adhesion.[5]

The I domain of α subunit contains a "metal-ion-dependent adhesive site (MIDAS)" site, which is responsible for binding divalent metal cations like $Mg^{2+}$. This site plays a vital role in protein-ligand interactions. When a ligand binds, it modifies how metal ion is coordinated, leading transitioning of the I domain from a closed, inactive state to an open, active form. This transition increases the affinity for the ligand and promotes further activation of the integrin. This activation process resembles that of small G proteins, where GTP hydrolysis results in changes to the coordination of $Mg^{2+}$ ion, leading to subsequent conformational changes.[4] (Figure 1)

### Integrin β subunit

The I-like domain makes up the β subunit and shares structural similarities with the I-domain found in α subunits. Additionally, it consists of a PSI domain, a hybrid domain, four EGF repeats, and a βTD domain near the cell membrane.[4]

Most human β subunits have cytoplasmic tails shorter than 75 amino acids, except for β4, which is significantly longer (around 1000 amino acids) and contains additional fibronectin type III repeats.[6]

In addition, the β subunit includes a crucial metal ion-dependent adhesion site (MIDAS) that coordinates $Mg^{2+}$, along with an adjacent site (ADMIDAS) that can bind $Ca^{2+}$. This binding can inhibit or activate the integrin depending on the metal ion present (e.g., $Mn^{2+}$ binding leads to a conformational change that activates the integrin).[3] The β subunit is essential for ligand binding, especially in α subunits that lack an I-domain.[4] (Figure 1)

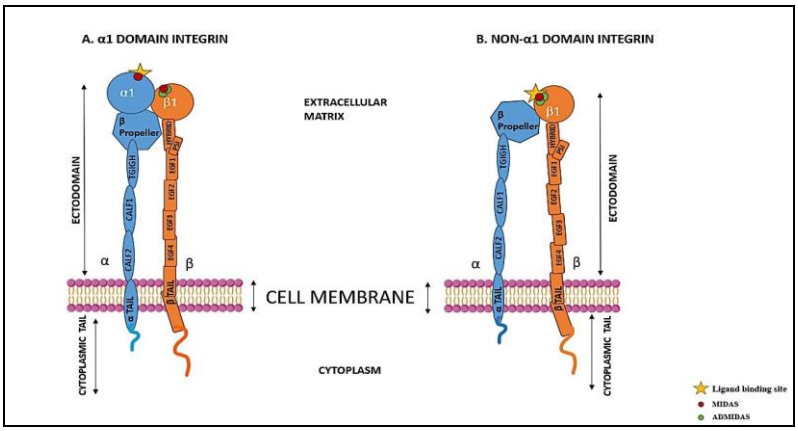


**Figure 1: Structure of integrin.**

## CLASSIFICATION OF INTEGRINS

Integrins are classified based on ligand specificity (Figure 2, Table 1).[5,6]

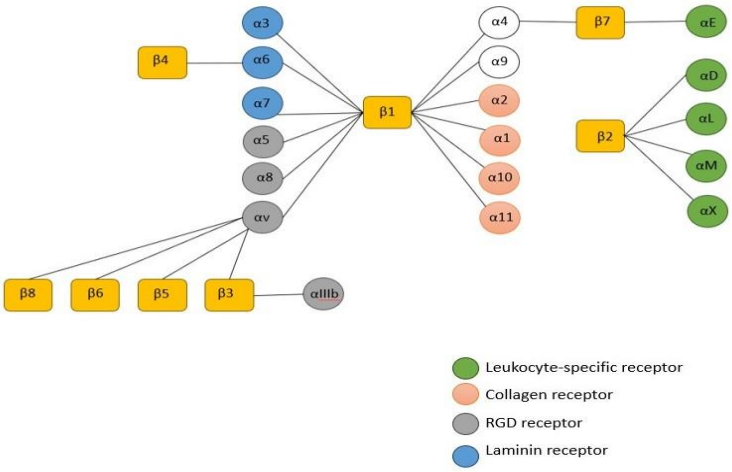


**Figure 2: The 18α and 8β subunits undergo heterodimerization to generate 24 different integrins that have an affinity for specific receptors, namely, leukocyte-specific receptors, collagen, RGD, and laminin receptors.**

**Table 1: Mammalian integrin αβ heterodimers can be broadly classified into four classes based on ligand specificity.**

| | |
|---|---|
| Leukocyte binding integrins | αLβ2, αMβ2, αXβ2, and αDβ2 |
| Collagen-binding integrins | α1β1, α2β1, α3β1, α10β1, and α11β1 |
| Arg-Gly-Asp (RGD) recognizing integrins | α5β1, αVβ1, αVβ3, αVβ5, αVβ6, αVβ8, and αIIbβ3 |
| Laminin-binding integrins | α1β1, α2β1, α3β1, α6β1, α7β1, and α6β4 |

**Table 2: Integrin α and β subunit combinations and their ligands.[2]**

| | | |
|---|---|---|
| β1 | α1, α2, α3, α4, α5, α6, α7, α8, α9, α10, α11, αV | collagens, laminins, Fibronectin, Merosin, TIMP-2, uPAR, vitronectin, angiostatin, Kalinin, tTG |
| β2 | αL, αM, αX, αD | ICAMs, iC3b, VCAM, Fibrinogen |
| β3 | αIIb, αV | Fibronectin, vitronectin, fibrinogen, collagens, vWf, thrombospondin, FGF-2, MMP-2 |
| β4 | α6 | Laminins |
| β5 | αV | Vitronectin, uPAR |
| β6 | αV | Tenascin-C, Fibronectin |
| β7 | α4, αE, αV | Fibronectin, VCAM, MAdCAM, E-cadherin |
| β8 | αV | Vitronectin, fibronectin |

(*TIMP-2: tissue inhibitor of metalloproteinase, uPAR: urokinase-type plasminogen activator (uPA) receptor, tTG: tissue-type transglutaminase, ICAM: intercellular cell adhesion molecule, iC3b: inactivated complement component 3b, VCAM: vascular cell adhesion molecule, vWf: von Willebrand factor, FGF-2: fibroblast growth factor 2; MMP: matrix metallo-proteinases and MadCAM: mucosal addressin cell adhesion molecule.)*

## INTEGRIN ACTIVATION

Integrins are characterized by their reversible and flexible conformational changes. In their resting state (inactive), the extracellular domains of integrins that bind to the ligand are bent, facing towards the membrane, with bounded intracellular tails. Activation leads to the integrin head extending, opening the ligand-binding site, and separating the intracellular tails. The αβ heterodimers of integrins can be found in three configurations, namely; bent-closed which is inactive, extended-closed and extended-open which are in active state with low and high affinity respectively. In a normal inactive state, integrins are unbound to ligands and maintain a bent shape. The balance among this different conformation is crucial for regulating cell adhesion affinity and signalling strength. Integrins uniquely transmit signals through the plasma membrane in both directions. They can initiate intracellular signalling upon ligand binding (outside-in signalling), while also being able to modulate their affinity for ligands based on internal signals (inside-out signalling).[4,8,7] (Figure 3)

**Inside-out signalling**

Signals from within the cell, particularly the signals from G-protein coupled receptors (GPCR) activate integrin by causing the phosphorylation of the β subunit's cytoplasmic domain. The interaction between α and β cytoplasmic tails is essential for keeping integrins in their inactive state. Chemokines can act as signals that disrupt the inactivated state of integrins, promoting their activation through pathways involving GPCR.

Activation leads to a straightening of the extracellular domains, exposing the ligand binding site. This allows integrins to bind their ligands effectively, facilitating outside-in-signalling.

Various cytoskeletal proteins, including α-actin, talin, vinculin, filamin, paxillin and tensin, interact with cytoplasmic tails but talin and kindlin, are particularly crucial for integrin activation. They bind to distinct regions of the β integrin tails and work together to promote the separation of these tails, enhancing integrin affinity for ligands.[4,5]

**Outside-in signalling**

Outside-in signalling in integrins is a critical mechanism by which cells communicate with their external environment. This process is initiated when integrins, which are transmembrane receptors, bind to extracellular ligands, such as components of the extracellular matrix (ECM) or other cells, they cluster in the cell membrane and transmit signals to the interior of the cell. Upon ligand binding a significant conformational change in the integrin structure observed that is the ligand-binding head extends, leading to outward movement of hybrid domain, separation of the alpha beta domains and the transmembrane domains separation.

The conformational shift allows the cytoplasmic tails of the integrin to interact with intracellular signalling proteins. This includes enzymes like focal adhesion kinase (FAK) and small GTPases (such as Rho and Rac), as well as adaptor proteins like paxillin. The binding of these intracellular signalling molecules activates various downstream signalling pathways. The affinity of integrin and its valence in binding ligands like cell adhesion molecule (CAM) regulate the extent of outside-in signalling at focal adhesive contacts, which transmit information about the density of extracellular ligands or extracellular forces on the cell.[5]

The reversible and dynamic transformation of integrins between non-adhesive and adhesive states is facilitated by such bidirectional signalling, which is crucial for controlling cell adhesion and migration.[5,8]

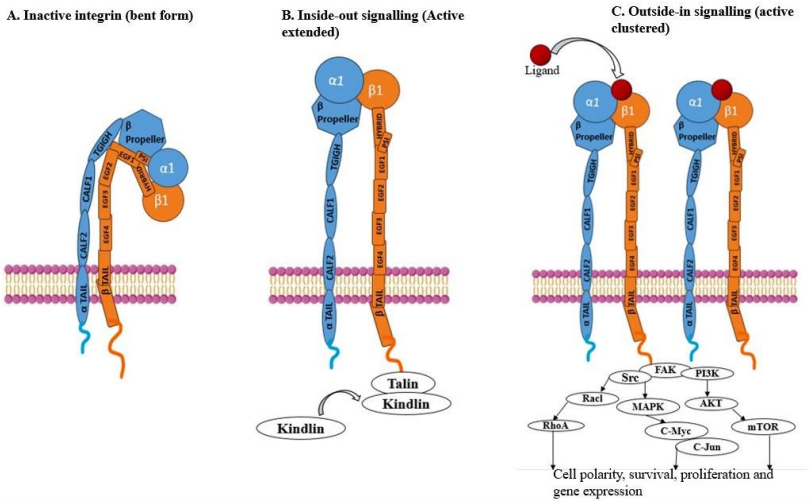


**Figure 3: Activation of integrin. The bent, active extended, and active clustered conformation of integrins signifies inactive integrin, inside-out signalling and outside-in signalling respectively.**

## INFLAMMATORY BOWEL DISEASE

Crohn's disease and ulcerative colitis are types of idiopathic inflammatory bowel diseases (IBDs), a chronic inflammatory disorder, caused by cytokine-driven mechanisms of the gastrointestinal tract, affecting individuals with impaired immunity. Excess production of IFN-γ/IL-19 and IL-12/IL-23 is linked to Crohn's disease, which affects the colon and small intestine and causes intermittent ulceration. while ulcerative colitis is primarily caused by increased production of IL-13 affecting the colon. It is characterized by a persistent mucosal inflammation that almost always affects the rectum and extends till proximal end.[10] Although the exact cause of IBD is unknown, the current consensus suggests that immunological dysregulation (which includes inappropriate lymphocyte activation, innate immune cell infiltrations like neutrophils), intestinal tract barrier malfunction, and lack of tolerance to resident gut bacteria which caused by a combination of hereditary and environmental factors.[11,14,21]

Specifically, the anomalies that underlie the pathophysiology of inflammatory bowel disease (IBD) are not limited to those that are mediated by traditional immune cells including lymphocytes of the T and B types, macrophages, and dendritic cells; they also include non-immune cells. It's interesting to note that endothelium has emerged as a key focus of research in gut inflammation. It is now widely acknowledged that endothelium actively contributes to the pathophysiology of inflammation because endothelial cells are essential for maintaining

mucosal immune homeostasis. They function as "guardians," controlling the quantity and quality of leukocytes that move from the intravascular space to the interstitial region.[12]

**Immune cells of the gut and their function**

Genetic risk factors for inflammatory bowel disease (IBD) are linked to disturbances in intestinal epithelial cells, particularly Paneth cells, which can cause inflammation. Intestinal macrophages play a vital role in homeostasis and reducing inflammation, though a certain subtype of them can potently induce inflammation in IBD.[13]

T lymphocytes, including regulatory T lymphocytes ($T_{reg}$) and memory T lymphocytes ($T_{mem}$), play a crucial role in regulating immune responses in the gut. Functional deficits in Tregs can increase inflammation by disrupting the balance between $T_{regs}$ and T effector cells ($T_{effs}$). CD4+ T lymphocytes, particularly in the gut, are recognized as essential for maintaining tolerance and inflammation balance. Innate lymphoid cells (ILCs) resemble lymphocytes but lack antigen-specific receptors. DCs serve as crucial for antigen presentation as well as T lymphocyte priming and activation. DCs are guardians of peripheral tissues, such as the colon, and they reside and drain lymph nodes, where they interact with T cells.[14]

Thus, Dendritic cells are able to induce and suppress intestinal inflammation by stimulating T cells and producing inflammatory mediators.[13]

A numerous treatment targets, including 5-aminosalicylic acid, non-specific immunosuppressants, corticosteroids, etc, have typically been used to treat intestinal inflammation. In recent years, alternative therapies, like target tumour necrosis factor (TNF)-α, have gained popularity. Despite being successful in many individuals, a considerable number of patients do not show remission. Highly selective inhibition of the compounds involved in recruiting leukocytes to the inflamed gut is regarded as one among the most intriguing alternatives to conventional IBD treatments.[15]

The immune system employs an intricate system that regulates tissues. Chemokines, adhesion molecules, and integrins have roles in leukocyte migration into intestinal tissues, to facilitate rolling along the endothelial cells of blood vessel, followed by arresting after integrin activation, binding to respective ligands (adhesion molecules), and transmigration to lamina propria. T lymphocytes in the peripheral circulation can reach the gut via an endothelial

barrier in two ways: either the naive T cells travel to GALT (gut-associated lymphoid tissue) or memory T cells enter the lamina propria through systemic circulation.[16]

Normal homeostatic conditions facilitate the migration of various leukocyte populations into the gut through interactions involving different integrins. Inflammation in the intestine can activate the intestinal vascular endothelium, leading to the upregulation of VCAM-1 and ICAM-1 expression. These cytokines can alter lymphocyte migration patterns. Different leukocyte populations express different integrins, including α4β1, α4β7, and αEβ7. These integrins react with CAMs in the immunoglobulin superfamily to induce cell adhesion. α4β1, α4β7, and αEβ7 integrins bind to VCAM-1 on vascular endothelial cells, MAdCAM-1 on intestinal endothelial cells, and E-cadherin on mucosal epithelial cells respectively.[16,17]

## INTEGRINS IN THE PATHOGENESIS OF IBD

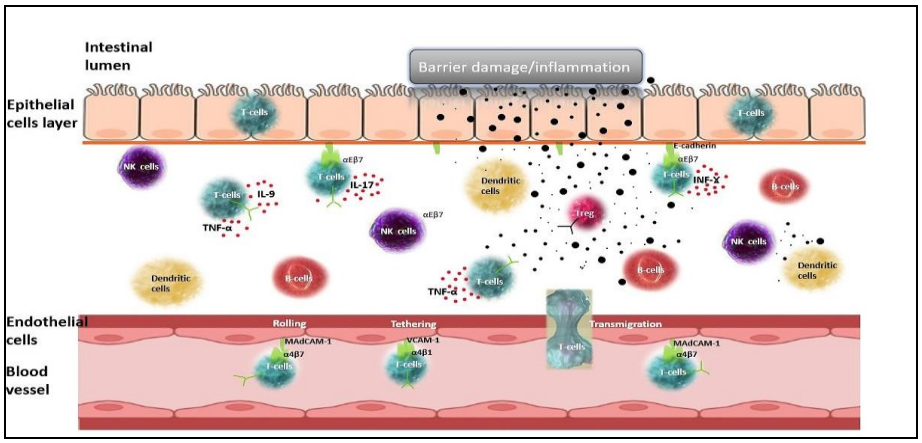


**Figure 4: The pathogenesis of IBD involve immune cells like T cells, DCs, NK cells with production of different cytokines or chemokines. Homing of immune cells to inflamed gut involves stepwise process like rolling, tethering and transmigration by interaction between the circulatory immune cells expressing integrins with CAMs of endothelial cells.**

The stages of a cell adhesion cascade. One characteristic of the chronic inflammation seen in the tissues affected by autoimmune diseases is a persistent build-up of leukocytes.[8] (Figure 4).

DCs take up antigens during an inflammatory response and move to lymph nodes, where they stimulate T cells that are specific to that antigen. T cells that have been activated go into the intestinal vasculature. Leukocyte rolling, leukocyte-firm adherence and trans-endothelial migration are the three processes by which leukocytes must interact with and pass an

endothelial monolayer lining on the inner side of the vasculature in order to accumulate in inflamed tissues.[8,12,14]

T lymphocyte migration is regulated by the initial display of receptors on microvilli, which leading to their tethering and rolling along the endothelial surface via selectins and their ligands. This mechanism takes place through high endothelial venules [HEVs] in GALT as well as post-capillary venules in the lamina propria [LP]. Leukocytes are slowed down by this rolling interaction and brought close to the inflammatory endothelial cells, where they enable the cells to detect chemokines that are supplied by the endothelium.[8,9]

Leukocytes undergo activation through chemokines while rolling, initiating an intracellular signalling cascade that affects the cytoplasmic domains of integrins. This process transforms inactive low-affinity integrins into a state of high affinity, capable of binding to ligands, which promotes the immobilization of rolling leukocytes and firm adhesion to inflamed endothelial cells, even under shear stress. Initially, it was believed that the sequence of interactions between leukocytes and endothelial cells included rolling mediated by selectins, chemokine-induced activation, and an increase in integrin affinity.[8]

Pro-inflammatory mediators such IFN-γ, IL-6, IL-9, and IL-17 are produced locally when effector T cells migrate to the inflammatory gut due to the interaction of α4β7 with MAdCAM-1 or α4β1 with VCAM-1. Upon reaching the lamina propria, these T cells might be retained because of increased interactions with E-cadherin and the surface αEβ7. Integrin-specific antibodies are currently aimed at targeting α4, α4β7, αEβ7, and MAdCAM-1.[14]

**Integrin α4β7 (LPAM-I)**

The α4 integrins, specifically α4β7 [also known as lymphocyte Peyer's patch adhesion molecule (LPAM-I)], is a type-I transmembrane glycoprotein consisting of α4 and β7 subunits. The ITGA4 gene encodes α4, which is a transmembrane protein forms a heterodimer with the ITGB7-encoded β7. The α4β7 expression is limited to or found exclusively in lymphocytes, NK cells, mast cells, basophils, and monocytes.[14 18 19]

The binding of $\alpha 4\beta 7$ with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) facilitates the movement of lymphocytes to the gut-associated lymphoid tissue (GALT). MAdCAM-1 is the primary natural ligand of $\alpha 4\beta 7$ and is mainly present on the luminal surface of high endothelial venules (HEV) in the intestinal mucosa as well as in Peyer's

patches. This interaction is crucial for monitoring the immune system of GIT and in the selective transportation of lymphocytes to the gut, allowing them to cross the vascular endothelial barrier to reach GALT or the intestinal lamina propria.[19,20,21]

**Integrin α4β1 (VLA-4)**

α4β1, also known as very late antigen (VLA)-4 is present on the majority of leukocytes and neutrophils made up of α4 & β1 subunits or components. The ITGA4 gene encodes α4, which is a transmembrane protein that forms a heterodimer with the ITGB1-encoded β1.[14,18]

VLA-4 plays a crucial role in leukocyte adhesion to fibronectin and VCAM-I, a cytokine-inducible endothelial cell ligand. It also aids in the homing or guiding of memory and effector T lymphocytes to inflamed tissues, such as the intestines, and other non-intestinal sites like the lungs and central nervous system. VLA-4's binding to VCAM-1 and fibronectin is expected to function in distinct steps of monocyte diapedesis.[18,21,22]

**Integrin αEβ7 (CD103)**

The αE integrin, also referred as CD103, is a transmembrane protein encoded by the ITGAE gene on chromosome 17 has the capability to dimerize with β7 integrin to form αEβ7, which can then attach to its ligand E-cadherin.[14,21]

αEβ7 is expressed in minimal amounts in circulating T cells but is prominently present in intestinal T cells, both within the LP and intraepithelial space. The expression of αE integrin has also been observed in dendritic cells (DCs), mast cells, innate lymphoid cells, and NK cells infiltrating tumors.[14,16]

Following the entry of lymphocytes into the gut, local tumor growth factor (TGF)-β is thought to trigger the expression of αEβ7 on the surface of T lymphocytes. Consequently, this enables lymphocytes to interact with and become embedded in the epithelium as intraepithelial lymph (IELs), leading to their retention in the intestinal lumen's epithelial layer.

CD8+ and Th9 lymphocytes also exhibit high expression of αEβ7 integrin. The role of Th9 cells in the pathobiology of IBD is increasingly recognized, as blocking IL-9 has been demonstrated to reduce disease severity in experimental models of IBD.[14]

## ANTI-INTEGRIN THERAPY

The dysregulation of integrins plays a significant role in the development of various diseases characterized by altered angiogenesis, inflammation, or infections. The treatment approaches can either focus directly on integrins or on their ligands. Among the 24 known human integrins, several have already been recognized as potential therapeutic targets for monoclonal antibodies, peptides, and/or small molecules.[6] (Table 4)

**Table 3: Various approved and under clinical trial anti-integrins for IBD treatment along with their indication and Adverse effects.**

| Drug | Class | Target | Description | Clinical studies | Indication | Adverse Effects | References |
|---|---|---|---|---|---|---|---|
| Natalizumab (Tysabri) | Humanised $I_gG4$ mAb produced in murine myeloma cells | α4β7 & α4β1 integrin | Natalizumab prevents the binding of α4b1 to VCAM-1 and α4b7 to MAdCAM-1. It hinders the recruitment of lymphocytes in the GALT. **ROA:** IV | ENACT-1<br>ENACT-2<br>ENCORE | Induction & maintenance in CD | High risk of PML. Other ADR includes Hepatotoxicity, Opportunistic infection Malignant melanoma | **[17, 23, 24, 25]** |
| Vedolizumab (Takeda) | Humanized IgG1 mAb<br><br>Vedolizumab is manufactured in Chinese hamster ovary cells | α4β7 integrin | Vedolizumab inhibits the interaction between α4β7-integrin and MAdCAM-1 selectively hinders lymphocyte trafficking in the intestine. **ROA:** IV | GEMINI 1<br><br>GEMINI 2<br>GEMINI 3 | Induction and maintenance in UC<br><br>Induction and maintenance in CD | Common ADE include nasopharyngitis Upper respiratory infection arthralgia Low risk of PML Opportunistic infection malignancy compare to Natalizumab. | **[9, 17, 20, 26]** |
| Etrolizumab | Humanized IgG1 mAb | α4β7 & αEβ7 integrins | Inhibiting the interactions between α4β7 and MAdCAM-1, as well as αEβ7 and E-cadherin, results in hinderance to leukocytes trafficking to the gut. **ROA:** IV & SC | HIBISCUS I & II<br><br>LAUREL<br><br>GARDENIA<br><br>HICKORY<br><br>COTTONWOOD<br><br>BERGAMOT | Induction of UC<br><br>Maintenance of UC<br>Induction & maintenance of UC<br>Induction & maintenance of UC<br>Open label extension for UC<br>Induction& Maintenance trail for CD<br>Open- label extension & safety monitoring | The most common adverse events (AE) were exacerbation of UC, headache, and nasopharyngitis. | **[17, 27, 28, 29, 30]** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | JUNIPER | for CD | | |
| Abrilumab | Fully human IgG2 mAb | α4β7-integrin | Targets a4b7 in a selective manner and prevents it from interacting with MAdCAM-1. Prevents the recruitment and extravasation of leukocytes from blood vessels as well as a specific subset of CD4+ T cells. **ROA:** SC | Phase IIb | Induction in UC & CD | No significant adverse effects reported | **[25, 27, 31, 32]** |
| AJM300 | Oral small molecule | α4 integrin subunit target (α4β7 & α4β1 | The administration of AJM300 was found to reduce T lymphocytes in the lamina propria, based on previous research conducted on animals. **ROA:** oral | Phase II a | Induction in UC | No serious adverse effects reported | **[9, 17, 27]** |
| Ontamalimab | Fully human monoclonal IgG2 antibody | α4β7 integrin | Block α4β7: MAdCAM-1 interaction and reduce leukocyte translocation and thereby mucosal inflammation. **ROA:** SC | TURANDOT I & II<br><br>OPERA I & II<br><br>TOSCA | Induction & Maintenance in UC<br><br>Open label extension trial in CD<br>Safety study in CD | No serious adverse effects reported | **[27, 33]** |

(*ROA: Route of administration; IV: Intravenous; SC: Subcutaneous; PML: Progressive multifocal leukoencephalopathy*)

## CONCLUSION

Integrins are a type of cell adhesion receptor that binds to soluble, cell-surface, and extracellular matrix ligands. Each of the α and β subunits has a unique domain structure, and their extracellular domains contribute to the heterodimer's ligand-binding site.

Integrins are involved in a variety of physiological processes, such as inflammation, healing of wounds, and cell growth and differentiation.

Tumor necrosis factor is a key mediator of inflammation in inflammatory bowel disease (IBD), but there are a number of additional mechanisms that trigger an inflammatory response as well. Leukocyte infiltration of the gastrointestinal tract is one such pathway. Because leukocytes in the systemic circulation migrate to inflammatory areas, inhibiting this pathway may be a key component of an IBD therapeutic strategy.

Anti-integrin treatments have gained interest as novel inflammatory bowel disease therapeutics. They prevent leukocyte extravasation by preventing the interaction of integrins on immune cells with endothelial CAMs (cell adhesion molecules).

There is ongoing medical interest in the development of integrin-based therapies since they have demonstrated clinically significant improvements in numerous patients. Nearly all anti-integrins currently being used or undergoing late-stage clinical trials aim to inhibit either the ligand or its binding site. Natalizumab, which has indications in multiple sclerosis and Crohn's disease, was the first successful medication against the α4 subunit of the integrin heterodimer.

But the unforeseen emergence of progressive multifocal leukoencephalopathy (PML) in natalizumab patients prompted a voluntary withdrawal of the medicine from the market in 2005. However, because it works well to treat multiple sclerosis, it was brought back to the market in 2006 under the rigorous TOUCH (Tysabri outreach: unified commitment to health) monitoring program.

Given safety concerns, the place for natalizumab in management of moderate to severe CD seems limited. Natalizumab is currently not approved for IBD in Europe.

In contrast to natalizumab, vedolizumab is used to treat both UC and CD and has been shown to have a lower incidence of PML opportunistic infection-related malignancies in both induction and maintenance therapy. According to the outcomes of the current trial, AJM 300, Ontamalimab, Abrilumab, and Etrolizumab are safe, well-tolerated therapies that do not cause any significant opportunistic infections.

A significant number of patients fail to reach clinical remission or lose the responsiveness to conventional intervention such as amino salicylates, glucocorticoids, and immunomodulators. So, biological medications that target pathways involved in inflammation switched conventional medications in the treatment of inflammatory bowel disease (IBD). Therefore, gut-specific anti-integrin therapies present a novel class of well-tolerated, safe, and efficacious medicines with significant promise for both UC and CD. However, immunogenicity with a loss of response, and invasive administration routes (subcutaneous or intravenous), among other drawbacks, which limit their use. To precisely understand how anti-integrin therapies work in IBD, further research is required.

IBD has an intricate pathogenesis. Accordingly, different patients may respond differently to a given treatment plan. A significant step toward individualized treatment can be made following a thorough evaluation of the patients.

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