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Integrins in Dermatology

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Abstract

Integrins are heterodimeric transmembrane glycoprotein composed of non-covalently linked α and β subunits. They are cell surface adhesion molecules essential for cell-matrix and cell-cell interaction and are capable of transmitting signals from within or from without the cell.

Integrins are important for epidermo-dermal anchorage. Genetic or autoimmune dysfunction of a6b4 results in blistering of skin and mucous membranes, like junctional epidermolysis bullosa with pyloric atresia and cicatricial pemphigoid respectively. Expression of different types of integrins on the surface of keratinocytes, fibroblasts, endothelial cells and blood cells is essential for wound healing.

In malignancy, increased expression of integrin promotes tumor growth and metastasis. Metastasis is promoted by integrins in three principle mechanisms, through stimulating cell migration, production of proteases and by increasing blood vessel formation.

Beta 2 integrins on leukocytes are important for their recruitment to sites of inflammation and infection. Genetic dysfunction of b2 subunit results in the immune deficiency syndrome known as leukocyte adhesion deficiency, characterized by inability of leukocytes to migrate and phagocytose. Beta 2 integrins also help in providing close contact for antigen presentation to T-lymphocytes and leukocyte activation. LFA-1/ ICAM-1 interaction between T-lymphocytes and somatic cells is seen in many immunologic skin conditions, such as contact dermatitis, psoriasis, lichen planus, vitiligo, scleroderma and others, which make them potential drug targets.

Introduction

Hynes in 1987[1] was the first to apply the term "***Integrin***" to describe a family of structurally, immunochemically and functionally related receptors, which ***integrated*** the extracellular matrix with the intracellular cytoskeleton to mediate cell adhesion and migration.

Integrins are molecules essential for cell-cell and cell-substrate adhesion. They are cell surface transmembrane glycoproteins that function as adhesion receptors transmitting biochemical and mechanical signals in a bidirectional manner across the plasma membrane and thus influence most cellular functions such as proliferation, differentiation, apoptosis and cell migration [2, 3]. Among a host of other adhesion molecules, including selectins, members of immunoglobulin superfamily, and cadherins, together, they participate in every cellular activity, although they may be latent, i.e. not expressed until the cell is stimulated, expressed very transiently or may be expressed for longer periods [4].

Integrins and their ligands play key roles in development, immune responses, leukocyte trafficking, and hemostasis. They share in the pathogenesis of many genetic, autoimmune and malignant diseases, and are the receptors for many viruses and bacteria. Hence, integrins are a promised target of future effective drugs [2, 5] .

A brief discussion of integrin structure, variable modes of action, important role in cutaneous health and disease, and their future role as drug targets will be presented.

Integrin Structure & Mechanism of Action

Structure:

Each integrin is a heterodimer composed of an alpha (α) and a beta (β) subunit that are stabilized by non-covalent bonds. On searching the human genome, 18 a and 8 b subunits have been recognized. Some limitations for dimer formation using certain α and β subunits exist resulting in the formation of only 24 different integrins [2, 6].

Although there are no genetic relations between α- and β-subunits, they share similarity in domain structure [7]. Each subunit contains three domains: a big glycosylated extracellular domain (consisting of more than 90% of the whole molecule), a hydrophobic transmembrane domain (responsible for membrane anchoring) and a

small cytoplasmic domain (.Figure 1). The size of α-subunits varies from 120-180kD, while that of β-subunits varies from 95-117 kD (8, 9].

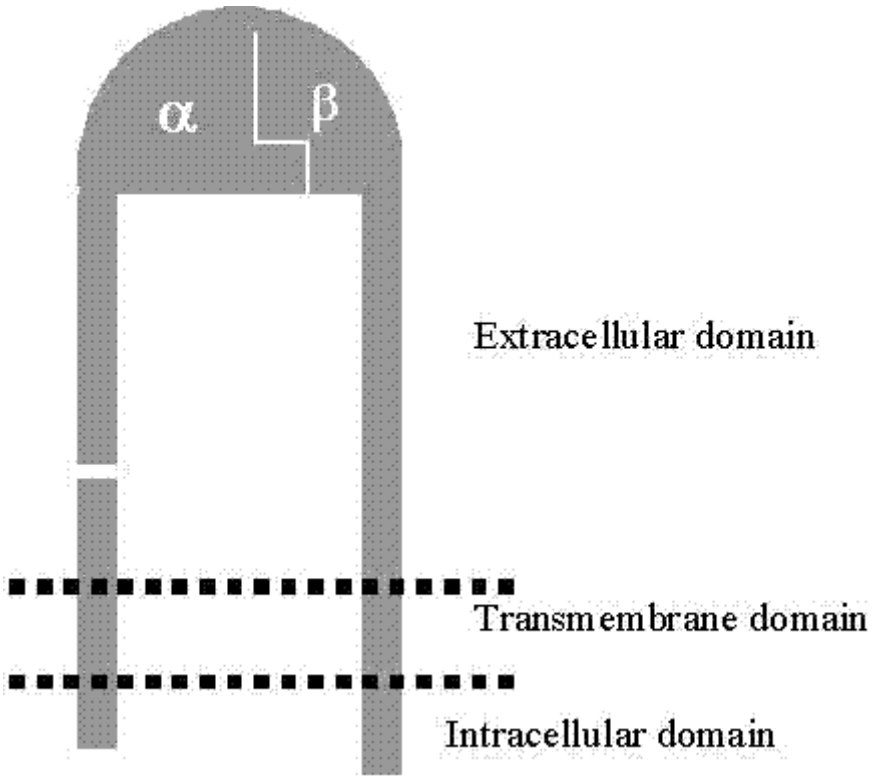

Figure 1 Integrin Structure, showing large extracellular domain and small cytoplasmic domain (20-50 amino acids for a- and 15-65 amino acids for b-subunits) The a-subunit complexes with b-subunit to form the ligand-binding "head", which is attached to two "legs", one from each subunit. The cytoplasmic domain is also referred to as the "tail" Modified from Berman et al., 2003[2]

Both subunits are required for ligand binding. This is consistent with the fact, that switching either subunit can change receptor specificity. Individual integrins can bind more than one ligand, and similarly, individual ligands are often recognized by more than one integrin so there is no absolute specificity (Table 1). This is related to the ability of integrins to recognize and bind to small specific oligopeptide sequences, such as RGD sequence (Arg-Gly-Asp) present on a number of ligands as fibronectin, vitronectin and other adhesion proteins [10]. Furthermore, the cytoplasmic domains play a primary role in ligand and signal properties of integrins and variability of these sites is a basis for the diverse functions of the whole integrin family and unique functions of certain receptors [6]. Many integrins are not constitutively active; they are in an "OFF" state, in which they do not bind ligands and do not signal. Integrin activation can occur from outside after

binding with its specific ligand "outside-in" signaling, or it can occur from inside "inside-out" signaling [11, 12].

Mechanisms of function of integrins

Cell Anchorage: Integrins were first known to be involved in cell anchorage to the extracellular matrix (ECM), linking it to the cytoskeleton [1]. The extracellular domain binds to ECM protein and the cytoplasmic domain links to cytoskeletal actin microfilaments. Certain linker proteins play an intermediate role in this binding activity, like talin and vinculin [10].

Integrins tend to be present in clusters like focal adhesions, which further serve to strengthen their attachment to the ECM and to concentrate messengers transducing signals from integrins and other cell receptors to the genome [2].

Signal Transduction: The second important function of integrins is their role in signal transduction. Both integrin subunits are needed for signal transduction. However, the β-subunit appears to have a more superior role, since most of cytoplasmic proteins bind to it [13, 14]. Stimulation of different signaling pathways depends on the type of integrin, type of ECM attached, and other diverse internal and external stimuli. External factors that stimulate integrins include cytokines, growth factors, chemokines, and adhesion molecules including other integrins[15] .

Integrins are involved in many aspects of cell behavior including proliferation, shape, polarity, differentiation, migration, and survival/apoptosis. Integrins mediate these functions through complex signaling pathways in which kinases, G-proteins, adapter proteins and proto-oncoproteins are involved [2]. The role of integrins in cell proliferation represents a good example illustrated in [16, 17].

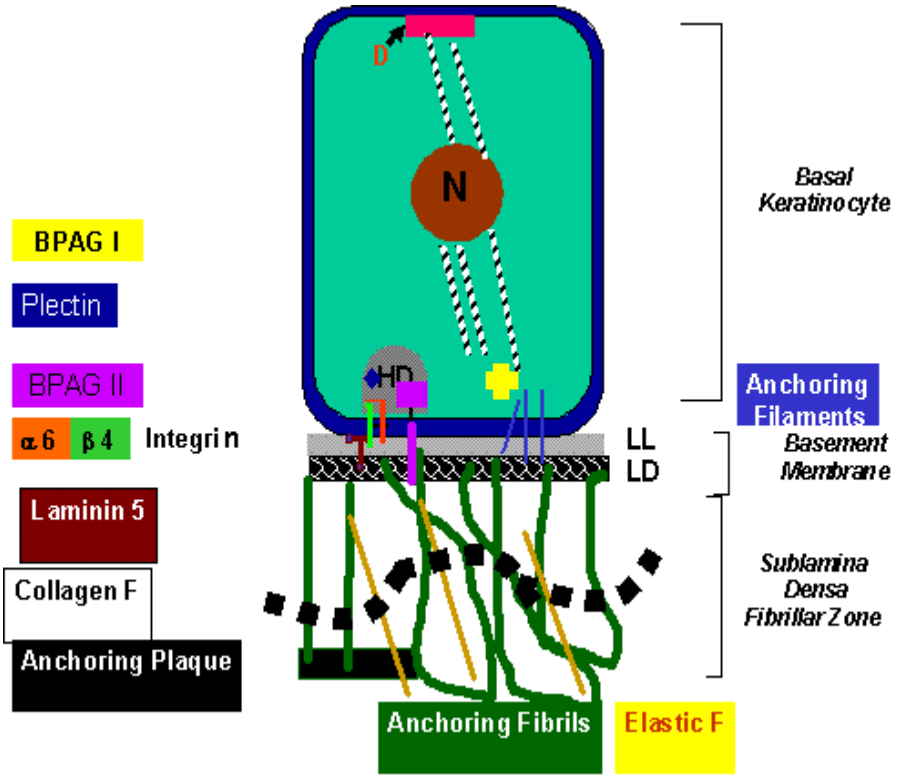

Figure 2. Epidermal Basement Membrane showing its molecular components (courtesy of MA Abdallah)

Role of integrins in development

Knockout mice for different integrin subunits show a different phenotype. The phenotypes range from complete block in preimplantation development, through major developmental defects and perinatal lethality to less severe functional defects [6]. Knockout of certain integrins that potentially bind to the same ligand, shows the relative role of each one, underscoring the similarities and differences in functioning. For example, mice lacking the gene for α1 and hence deficient in the collagen binding integrin α1 β1 maintained viability and fertility, but showed dermal hypoplasia and reduction of proliferation activity. However mouse embryos deficient in α2 subunit involved in the other collagen binding integrin α2 β1 die at the stage of implantation [2].

Role of integrins in proliferation, differentiation and apoptosis

Most normal cells do not divide when present in suspension; they need to be anchored to a solid substrate. This is mediated via integrins, which provide both binding and transduction of essential signals. For epidermal differentiation to occur, a downregulation of the laminin binding integrins α6β4 and α3β1 integrins is demonstrated [18, 19].

Cell anchorage also seems inhibitory to cellular apoptosis, integrin binding regulate apoptosis by their bifunctional capability in anchorage and signaling [20].

Keratinocyte Integrins

Keratinocytes exhibit a number of integrins, which are essential for their anchorage and migration. Some of them are constitutively expressed, while others are expressed or upregulated upon stimulation by wounding, pathological changes, or in culture. The most abundant constitutive integrins in the epidermis are α6β4, α2β1 and α3β1. Alpha v beta 5 is also a constitutive epidermal integrin, but is expressed at lower levels than the others. Alpha5 beta1 and αvβ6 are induced in culture and on wounding, while α9β1 is expressed in low concentration in undamaged epidermis and is upregulated during wound healing. Two other integrins have been found in epidermis; α8β1, which is confined to the arrector pili muscle and αvβ8, which is the only integrin found in normal suprabasal epidermis[21] (Table1).

Integrins of the normal undamaged epidermis are confined to the basal layer and outer root sheath of the hair follicle. Alpha 6 beta 4 is confined to hemidesmosomes, while other integrins are distributed over the basal, lateral, and apical surfaces of basal cells. Beta 1 integrins in the basal aspect of basal cells are present in clusters interspersed with hemidesmosomes, but the majority of β1 integrins appear to form an 'O' ring at the cell periphery [20].

Alpha6 Beta4 Integrin

Alpha6 Beta4 Integrin and Hemidesmosomes

In normal human keratinocytes, α6 and β4 subunits combine exclusively with each other. The integrin α6β4 is restricted to the basal surface of resting epidermal cells confined to hemidesmosomes. Other components of the hemidesmosomes include plectin, bullous pemphigoid antigen type 1 (BPAG1, 230 kD), bullous pemphigoid antigen type 2 (BPAG2, 180 kD) and CD151 tetraspanin [8, 22] (figure 2).

The general structure of α6β4 is the same as for other integrins. The exception lies in the big cytoplasmic portion of the b4 subunit (about 1000 amino acids), which binds keratin intermediate filaments instead of actin. Absence of this big cytoplasmic tail prevents hemidesmosomal assembly. The membrane proximal region of the cytoplasmic domain of the β subunit directly associates with plectin, while its distal region binds BPAG2 and BPAG1 [21]. The proximal extracellular domain of the α subunit binds a region on BPAG2, and is

responsible for localizing it to hemidesmosome [5, 23].

Laminin 5 and laminin 1 are the preferred extracellular ligands for α6β4 [24]. Laminin 5 (epiligrin, kalinin) is the major laminin in epidermal basement membrane (figure 2). Both laminin 5 and α6β4 integrin are localized to anchoring filaments, where laminin 5 further links integrin directly to type VII collagen of anchoring fibrils and indirectly to other components of the lamina densa[18]. Integrin α6β4 and laminin 5 play a crucial role in the proper assembly of hemidesmosomes, as deficiency of either protein leads to impaired hemidesmosome formation. Alpha 6 beta 4 integrin is also important in stabilization of the dermal-epidermal junction by connecting the intermediate filaments with the ECM [25].

Alpha6 Beta4 Integrin and Cell Migration

Although α6β4 is primarily responsible for cell anchorage, it was found to be involved in cell migration and invasion,

which are important for wound healing and tumor progression. It has been detected on the leading edge of migrating keratinocytes in association with filamentous actin [26]. The role of α6β4 in migration and invasion implies changes in mechanical [25, 27**],** as well as signaling properties of the integrin [28, 29], which are combined with structural changes of laminin 5 as well as changes in the localization of laminin 1 and 5 [25, 30]. Migration could be mediated by growth and chemotactic factors [29].

Diseases due to malfunction of Alpha6 Beta4 Integrin

Junctional Epidermolysis Bullosa with Pyloric Atresia

Junctional epidermolysis bullosa with pyloric atresia (JEB-PA) is an autosomal recessive disorder resulting from mutations in genes encoding either α6 [31] or β4 integrin subunits [32]. Clinically, it is characterized by mucocutaneous fragility and gastrointestinal atresia, which most commonly affects the pylorus. Additional features of JEB-PA include involvement of the urogenital tract, aplasia cutis, and failure to thrive. While most affected individuals have a poor prognosis resulting in death in infancy (lethal type), others have milder clinical features and a better prognosis (non-lethal type) [33].

Absence of either integrin subunit results in ultrastrucurally abnormal hemidesmosomes with absent or decreased immunostaining of the respective, or even both integrin subunits at the basement membrane zone [31, 32, 34].

Cicatricial Pemphigoid

Cicatricial pemphigoid is a heterogeneous group of autoimmune subepidermal blistering diseases characterized by a predominant involvement of the external mucosal surfaces and a tendency to scarring. It is associated most commonly with autoantibodies to bullous pemphigoid 2 (BPAG2) and less frequently with those to laminin 5 or type VII collagen. In addition, a few cases have been described with autoantibodies to the β4 integrin subunit. These patients present with predominant ocular involvement [35].

Alpha 3 beta 1

The integrin α3β1 is predominantly expressed in basal keratinocytes, between hemidesmosomes as well as laterally, where it shares in epidermal-dermal cohesion [36]. It binds primarily to laminins, especially laminin 5, and in certain situations it can bind to collagen and fibronectin. When laminin 5 of resting keratinocytes binds α3β1, it inhibits keratinocyte migration. Their binding also regulates cellular proliferation and differentiation [23]. During wound healing, however, laminin 5 promotes keratinocyte migration. This occurs secondary to its cleavage by matrix metalloproteinase 2 (MMP-2, a gelatinase) released from activated epithelial cells [37].

Alpha2 beta 1

Alpha 2 beta 1 is a collagen receptor expressed by keratinocytes in abundance. It mediates keratinocyte migration over collagen during cutaneous wound repair. Epidermal growth factor (EGF) and transforming growth factor α (TGFα) upregulate α2β1 expression, further enhancing their motility [38]. Once α2β1 binds type I collagen, epidermal cells respond by producing collagenase (MMP-1). This enzyme is required for epidermal migration over collagen. [39]. In migrating cells, α2β1 moves from the lateral aspect of the cell to the very tip of the migrating edge [5].

Alpha 5 beta 1

Alpha 5 beta 1 is the classic fibronectin receptor that is expressed by keratinocytes only during wound repair. This integrin appears to be involved in keratinocyte motility [40]. Fibronectin is a multifunctional protein that is deposited early during wound healing as a part of the provisional matrix. Fibronectin together with TGFβ induce the expression of α5β1 on keratinocytes, making them capable of migration on the provisional matrix [41]. When activated by

fibronectin fragments, α5β1, in its turn, stimulates the synthesis of collagenase (MMP-1), stromelysin (MMP-3) and gelatinase (MMP-9) [42].

Alpha v integrins

Vitronectin is one of the provisional matrix proteins deposited at sites of injury. In most cells, the only integrins that bind to vitronectin contain an αv subunit [11]. Epidermal cells express αvβ5 as they migrate over provisional matrix containing vitronectin during re-epithelialization of cutaneous wounds [41].

Another αv receptor expressed by wound epidermis is αvβ6. It is a tenascin and fibronectin receptor rather than a vitronectin receptor [23]. During the first few days of migration the basal epidermal cells express αvβ5, while αvβ6 is present around the time of fusion. This timed expression is related to the presence of vitronectin early and tenascin later during healing [43].

Integrins and Wound Healing

Wound healing is a complex, ordered process, which occurs after tissue injury, in an attempt of the body to regain its integrity. Keratinocytes, fibroblasts, endothelial cells and blood components are involved in wound healing. Integrin receptors are required for all phases of wound repair [5]. All steps follow a specific time sequence, and can be temporally classified into inflammation, tissue formation, and tissue remodeling. These phases of wound repair, however, are not mutually exclusive but rather overlapping in time [44].

Inflammation

Injury to blood vessels stimulates intrinsic and extrinsic coagulation cascades. Successful hemostasis depends on platelet adhesion and aggregation. Platelets also release mediators and adhesive proteins including fibrinogen, fibronectin, thrombospondin and von Willebrand factor. The first three act as ligands for platelet aggregation, while von Willebrand factor mediates platelet adhesion to fibrillary collagens [45]. Platelet adhesion to all four proteins is mediated through αIIbβ3 and other surface integrins. Alpha IIb beta3 also mediates platelet driven clot retraction [46] .

Neutrophils followed by monocytes begin to emigrate into injured tissue. Both types of cells are recruited by chemotactic factors released in the injured area and their migration is facilitated by β2 integrins (CD11/CD18 and other surface proteins [47]. Infiltrating neutrophils attempt to clear the area of foreign particles, including bacteria. Effete

neutrophils in the wound are either extruded with the eschar or phagocytosed by macrophages or fibroblasts [44].

Once in tissue, monocytes progressively activate and phenotypically become macrophages. This occurs secondary to integrin binding to the ECM, which also stimulates signal transduction followed by the secretion of cytokines such as colony stimulating factor, tumor necrosis factor a (TNF a), and platelet-derived growth factor (PDGF). Such growth factors are necessary for initiation and propagation of new tissue formation in wounds [48].

Binding of monocytes or macrophages to specific ECM proteins through integrin receptors also stimulates ECM phagocytosis and Fc- and C3b-mediated phagocytosis. Thereby macrophages are armed to debride tissue through phagocytosis and digestion of pathogenic organisms, tissue debris, and effete neutrophils [5, 44].

Tissue Formation

Re-establishing a cutaneous cover

Basal keratinocytes from residual epithelial structures undergo morphological changes, lose their firm attachment with the basement membrane, and attain a migratory phenotype expressing migration-related integrins [5, 44]. The migrating wound epidermis does not simply transit over a wound coated with provisional matrix but rather dissects through the wound, separating desiccated or otherwise nonviable tissue from viable tissue [49]. The path of dissection appears to be determined by the array of integrins that the migrating epidermal cells express on their cell membranes. Since $\alpha v\beta 3$, the receptor for fibrinogen/fibrin and denatured collagen, is not expressed on keratinocytes, keratinocytes do not have the capacity to bind to this matrix protein [50, 51]. Hence the migrating wound epidermis avoids the fibrin-rich clot and migrates over dermal type I collagen permeated with fibronectin, vitronectin and tenascin, utilizing $\alpha 2\beta 1$ collagen receptors, $\alpha 5\beta 1$ fibronectin receptors, $\alpha v\beta 5$ vitronectin receptors, and $\alpha v\beta 6$ tenascin receptors, respectively [41].

As mentioned earlier, $\alpha 6\beta 4$ and $\alpha 3\beta 1$ contribute to cell migration over laminin after inducing structural changes within laminin [26, 37]. Migrating epidermal cells secrete plasminogen and plasminogen activator [39], in addition to MMPs secreted on integrin binding with their ECM ligands, in order to dissect their path through the provisional matrix [42].

Re-establishing a Dermal Integrity

Migrating monocytes, fibroblasts and newly forming blood vessels use integrin receptors that recognize provisional matrix, which is composed of fibrin, fibronectin, and vitronectin. Moreover, binding of ECM to integrin receptors provides signals for gene expression necessary to modulate cellular functions and secrete substances essential for wound healing [11, 44]. PDGF, TGFa and TGFb act in concert with each other to stimulate fibroblast proliferation, migration into the wound and later protein synthesis and wound retraction to occur [52].

PDGF stimulates the expression of different integrins on fibroblasts according to the type of the extracellular matrix environment, thereby promoting cell migration [12, 52, 53]. In addition, integrin binding to ECM stimulates the secretion of proteases to help fibroblasts dissect their path through the blood clot [44].

Once the fibroblasts have migrated into the wound, they start depositing loose ECM, composed of great quantities of fibronectin, followed by the deposition of abundant fibrillar collagen I, III and VI. As soon as a collagen matrix is deposited, fibroblasts remodel it by wound contraction. This occurs when fibroblasts assume a myofibroblast phenotype [54]. Fibroblasts link to the extracellular fibronectin matrix mainly through $\alpha 5\beta 1$ to collagen matrix through $\alpha 1\beta 1$ and $\alpha 2\beta 1$ collagen receptors; and to each other through direct adherens junctions [55]. New collagen bundles join end-to-end with collagen bundles at the wound edge. These links provide a network across the wound whereby the traction of fibroblasts on their pericellular matrix can be transmitted across the wound [5].

Neovascularization

During wound healing, angiogenic capillary sprouts invade the fibrin/fibronectin-rich wound clot and within a few days organize into a microvascular network throughout the granulation tissue. Endothelial cell migration and capillary formation is mediated by the binding of $\alpha v\beta 3$ expressed on their surface [56, 57].

Tissue Remodelling (Transition from provisional matrix to collagenous scar)

Endothelial cells followed by myofibroblasts and macrophages undergo programmed cell death (apoptosis), ultimately leading to a rather acellular scar. Over the ensuing weeks, fibronectin and

hyaluronic acid disappear; collagen bundles grow in size, increasing wound tensile strength; and proteoglycans are deposited, increasing wound resilience to deformation [44].

Integrins and Inflammation/ Immunity

Integrins important in the interaction of leukocytes with the endothelium fall into three groups: Beta2 integrin family (designated CD11/CD18) is composed of αLβ2 (CD11a/CD18, leukocyte function associated antigen-1, LFA-1), αMβ2 (CD11b/CD18, Mac-1), αXβ2 (CD11c/CD18, p150, 95) and αDβ2 (CD11d/CD18)[4, 47]. These four integrins demonstrate some sort of cell type and ligand specificity. While the first three are distributed on neutrophils and monocytes, B- and T-lymphocytes express only LFA-1, and eosinophils express p alone. Similarly, they share some but not all ligands. LFA-1 binds to all three members of the ICAM family (ICAM-1,2,3), Mac-1 binds only to ICAM-1, but additionally binds complement receptor iC3b (CR3), fibrinogen and factor X, binds to iC3b and fibrinogen, while CD11d/CD18 binds preferentially to ICAM-3 [58]. ICAM-1 expression is induced on endothelial cells and other cells by inflammatory cytokines, but ICAM-2 is constitutively expressed and therefore may be more important in lymphocyte recirculation that occurs in uninflamed skin [5].

Two α 4 integrins are important in leukocyte/endothelial cell interactions: α4β1 (very late antigen-4, VLA-4) and α4β7. While both of these integrins are present on B- and T-lymphocytes, VLA-4 is also expressed on monocytes and eosinophils. It binds to vascular cell adhesion molecule-1 (VCAM-1). VCAM-1 is expressed on the endothelial cells by cytokines [5]. VLA-4 binds also to fibronectin. Alpha 4 beta 7 binds mainly to the mucosal addressin cell adhesion molecule (MAdCAM) in addition to its capability to bind to VCAM-1 and fibronectin (Table 1) [47].

Lastly, αEβ7 integrin is expressed on lymphocytes [47] and binds E-cadherin on epithelial cells [10].

Role of integrins in inflammation

Leukocytes flow in the middle of the blood stream. When they are needed; they approach the blood vessel margin under the effect of shear
forces [4]. This is followed by tethering and rolling, arrest, adherence and lastly emigration of leukocytes through the blood vessel wall These events occur mostly in postcapillary venules, owing to their

high expression of adhesion molecules [4, 5] and could be summarized as follows:

Tethering and rolling

Tethering is mainly mediated by selectins [47]. L-selectin on leukocytes binds to its receptors (CD34 and glycosylation-dependent cell adhesion molecule-1 [GlyCAM-1]) on endothelial surface, followed by cleavage and L-selectin shedding [59]. Concomitant with the increased avidity of L-selectin is increased expression of β2 integrin, which at this stage is not yet activated. P-selectin of endothelial and plasma cells is rapidly mobilized to the plasma membrane and binds transiently to neutrophils and monocytes, contributing to their rolling [4, 60]. E-selectin is produced under the effect of IL-1, TNFα, lipopolysaccharide, substance P and mast cell degranulation on the surface of endothelial cells [61]. E-selectin binds to cutaneous leukocyte antigen (CLA) on lymphocytes and to specific carbohydrate residues on neutrophils [47].

Arrest and adhesion

Integrins of mobile, non-activated leukocytes do not bind to endothelial cell ligands, thus avoiding spontaneous cell aggregation and vascular damage. The classical chemoattractants (C5a, platelet activating factor, leukotriene B4 and N-fromyl peptides) stimulate neutrophils, monocytes and eosinophils with minimal cell type specificity. Chemokines, which are divided into two subfamilies, CXC and CC show more specificity. CXC chemokines like IL-8 act on neutrophils and fibroblasts involved in wound healing; while CC chemokines like MCP (monocyte chemotactic proteins) act on monocytes, eosinophils and lymphocyte subpopulations [58].

Binding of chemoattractants to specific leukocyte transmembrane receptors activates adhesiveness of integrin receptors on the surface, the second step in the process of recruitment [5]. LFA-1 and Mac-1 show conformational changes and increase in ligand binding sites after activation of the cell with resultant binding to their endothelial ligands (Table1). Leukocyte arrest at the site is followed by emigration or local inflammatory change. Activation of LFA-1 by binding to ICAM-1 stimulates a number of phosphorylation events, which further stabilize leukocyte adhesion to endothelium. Activation of integrins also stimulates cell synthesis of cytokines and receptors to chemokines contributing to cell emigration [79].

Emigration

Leukocytes leave vessels through inter-endothelial cell junction. The molecular mechanisms of leukocyte transmigration involve CD31, which is expressed both by leukocytes and endothelial cells, and interacts with itself. CD31 of activated lymphocytes could displace CD31-CD31 homophilic binding at endothelial junctions [47].

Role of integrins in cutaneous immunity

LFA-1 in antigen presentation

Antigen processing and presentation by antigen presenting cells (APC), like Langerhans cells, to T-lymphocytes is a prerequisite for T-cell activation. Antigen is presented in conjunction with class I or II major histocompatibility complex (MHC-I or II) to T-cell receptor (TCR), which is complexed with CD3 (TCR/ CD3 complex). TCR recognition of antigen bound to MHC is insufficient to lead to T-cell proliferation or effector function. There is a requirement for additional "co-stimulatory" signals. This involves close cell-cell contact mediated by several different adhesion molecules on either cell in addition to stimulatory cytokines, notably IL-1 and IL-2. Among the recognized adhesion molecules is binding of LFA-1 on T-cells to ICAM-1 on APC. The classical example of APC/ T-cell interaction is the afferent phase of allergic contact dermatitis, which demonstrates increased ICAM-1 expression on Langerhans cells as well as on keratinocytes [4].

Role of integrins in some dermatoses

Beside antigen presentation, interaction between ICAM-1 and its ligand LFA-1 is a necessary step for contact-dependant immunologic reactions via leukocytes [63]. LFA-1 expression is increased on lymphocytes and ICAM-1 is expressed on vascular endothelial cells at sites of inflammation as well as on keratinocytes, fibroblasts or melanocytes in a number of immunologically mediated skin conditions. In psoriasis [64], lichen planus [65], actinic prurigo [66] ICAM-1 is expressed on keratinocytes and/or Langerhans cells. ICAM-1 is expressed on melanocytes at the margin of active vitiligo lesions [67], while it is expressed on fibroblasts in cases of scleroderma [68]. ICAM-1 expression on keratinocytes and melanocytes and its upregulation on endothelial cells are induced by

several inflammatory cytokines such as IFN-γ, TNFa, IL-1, IL-6 and IL-7 [5, 47, 63, 69]. The expression of ICAM-1 is usually associated with the presence of an activated inflammatory infiltrate nearby, which contributes to the production of inflammatory mediators and probably to the pathologic changes that result.

Allergic contact dermatitis (ACD)

Beside the role played by LFA-1 in the afferent or sensitization phase of ACD mentioned before, a further role of integrins is evident during the efferent or effector limb. Antigen specific memory T-cells and other inflammatory cells invade the skin to cause the response clinically recognized as ACD [70]. Skin-homing memory Th1-cells express LFA-1, a4b1 and CLA, which interact with their corresponding ligands ICAM-1, VCAM-1 and E-selectin, expressed on endothelial cells until they migrate out of the blood vessels. Inflammatory cytokines and chemokines regulate the process, and among a number of effects, induce ICAM-1 on epidermal cells [59, 60]. LFA-1+ T-cells then head toward the ICAM-1+ epidermal cells. They secrete IL-2, and IFN-gamma and other cytokines, which activate cytotoxic T-cells, natural killer cells, macrophages and mast cells. The collection of all these cells with their mediators is responsible for epidermal spongiosis and dermal infiltrate, which are the histologic marks of ACD [70].

Psoriasis

Psoriasis is unique because it represents excessive but controlled cellular proliferation and inflammation. The exact pathogenetic mechanisms remain unclear, however it is now regarded as T-cell dependent disease. Th1 cells are recruited in a manner comparable to that of ACD. Psoriatic keratinocytes express ICAM-1 and MHC-II in response to cytokines produced by T-cell [64].

There is increased expression of a3, a5 and a6 b1 integrins in suprabasal position [71]. Suprabasal integrin expression is associated with epidermal hyperproliferation and could contribute to the onset of psoriasis [72, 73, 74].

Leukocyte Adhesion deficiency (LAD)

Two types of leukocyte adhesion deficiency (LAD) have been recognized, which share common clinical manifestations. The first, LAD1, is a rare autosomal recessive disorder. It results from deficiency of β2 integrin, leading to absence or deficiency of LFA-1, Mac-1 and p150,95 from the surface of neutrophils, monocytes and lymphocytes, which show impaired chemotaxis and phagocytosis [75].

LAD2 results from genetic defect in fucose synthesis, which is a constituent of the ligands for P- and E-selectin [5].

Patients with LAD1 have frequent skin infections, mucositis, and otitis. The skin infections often present as necrotic abscesses that resemble pyoderma gangrenosum, but the inflammatory response and production of purulent material are impaired. Patients may have delayed separation of the umbilical cord. Cellulitis of the face and perirectal area is common. Gingivitis with periodontitis results in loss of teeth. Life-threatening severe bacterial or fungal infections may occur. Poor wound healing leads to paper-thin or dysplastic cutaneous scars [75].

The severity of clinical involvement is proportional to the degree of glycoprotein deficiency. Patients with complete deficiency (0-2% expression) die by 2 years of age of overwhelming sepsis, while those with partial deficiency (10-20% expression) usually survive into adulthood[5]. Bone marrow transplantation represents the current treatment option. The normal CD18 subunit gene has been introduced into hematopoietic stem cells and may provide the basis for future gene therapy [75].

Integrins and Cutaneous Malignancy

Integrins may promote tumor growth directly through their increased expression on the surface of tumor cells. These integrins facilitate cell growth by induction of proliferative signaling pathways and/or by facilitating the invasion of their surroundings. Indirectly, increased integrin expression on blood vessels associated with tumors, may enhance their growth by facilitating angiogenesis. Since tumorigenesis is a multi-step process, the timing of altered integrin expression may be critical, and early changes may have a greater effect on the course of the disease than the pattern of integrin expression that characterizes the mature tumor [23]. Thus all malignancies, including those related to the skin bear variable forms of integrin expression. Discussed below are squamous cell carcinoma and malignant melanoma because of their relevant importance to the dermatologist.

Squamous cell carcinoma

Squamous cell carcinoma reveals considerable variation in integrin expression within the same tumor and between different tumors. Normal expression, overexpression and focal or extensive loss of expression of the major keratinocyte integrins have all been

observed, together with de novo expression of other integrins including αvβ6[23].

Normally, α6β4 integrin disappears as keratinocytes differentiate and move upwards in the epidermis. Increased α6β4 integrin expression correlates with a high risk of tumor progression in stratified squamous epithelia [76]. Alpha 6 beta 4 overexpression in suprabasal keratinocytes has been associated with poor prognosis in human oral cancer [77]. Within a given tumor, both overexpression of α6β4 in the suprabasal layers and focal loss at the tumor margin could be observed [76, 78].

On the other hand, expression of α6β4 is maintained in many invasive carcinomas in the absence of hemidesmosomes where it is associated with the actin cytoskeleton and promotes migratory capability of carcinoma cells [79].

Malignant Melanoma (MM)

Increased expression of αvβ3 was reported in malignant melanoma (MM), undifferentiated neuroblastoma, highly metastatic breast carcinoma and prostatic adenocarcinoma cell lines, which suggests its role in promoting rapid growth and metastasis of aggressive tumors [5]. This role is supported by two basic biological observations: αvβ3 ligates provisional matrix proteins such as fibronectin, fibrin, vitronectin and thrombospondin, that are deposited in the inflammatory sites around tumors; and αvβ3 binds and activates certain cell-surface-associated MMPs, which facilitate degradation of ECM and tumor progression [80]. In MM as in other aggressive tumors, the need for a good vascular supply is mandatory for their growth and metastasis. Increased expression of the angiogenesis marker, αvβ3, on endothelial cells supplying MM has been implicated in tumor growth and sustenance [81]. Other than αvβ3, integrins of the β1 family expressed on MM cell lines have been implicated in tumor metastasis [82, 83, 84].

Integrins as Potential Drug Targets

The elucidation of the role of inflammatory cells, their soluble mediators, adhesion molecules and signal transduction pathways in the pathogenesis of diseases, helped in the development of new targeted therapies, also known as ***biologics***. T-cell mediated diseases have received particular attention. As regards dermatological diseases,

extensive research has focused on psoriasis, a T-cell mediated disease [64].

Among the new therapeutic modalities, efaluzimab is directed against CD11a or the α-integrin subunit of LFA-1 [85]. Efaluzimab (Raptiva) is a humanized monoclonal antibody indicated for moderate to severe psoriasis. During efaluzimab treatment, T-cell CD11a was downregulated, together with histological evidence of epidermal thinning, decreased number of epidermal and dermal CD3+ T-cells, decreased T-cell CD11a availability, and decreased keratin 16 and ICAM-1 expression [85].

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