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Adhesion Receptors in Health and Disease

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ABSTRACT: Cell adhesion molecules have been recognized to play a major role in a variety of physiological and pathological phenomena. They determine the specificity of cell-cell binding and the interactions between cells and extracellular matrix proteins. Some of them may also function as receptors that trigger intracellular pathways and participate in cellular processes like migration, proliferation, differentiation, and cell death. The receptors that mediate adhesion between epithelial cells that are discussed in this review include integrins, selectins, the immunoglobulin superfamily members, and cadherins. The intent of this review is to inform the reader about recent advances in cellular and molecular functions of certain receptors, specifically those that are considered important in cell adhesion. We have deliberately not provided all-inclusive detailed information on every molecule, but instead, have presented a generalized overview in order to give the reader a global perspective. This information will be useful in enhancing the reader's understanding of the molecular pathology of diseases and recognizing the potential role of these receptors and ligands as therapeutic agents.

Key words. Cell adhesion molecules, integrins, cadherins, selectins, immunoglobulin superfamily.

Introduction

Advances in the treatment of human diseases rely upon the investigators' understanding of the pathophysiology of the disease process. Current understanding has moved from an organism level to the molecular level. The recent exponential growth of information about complex and heterogeneous human molecules has provided knowledge of various processes that facilitate, augment, alter, or disrupt cell functions. This is in large part due to advances in molecular biology and the application of its technology.

Recently, there has been a great interest in the study of several molecules that mediate cell adhesion. These adhesion receptors are usually transmembrane glycoproteins that mediate binding interactions on the cellular surface. They determine the specificity of cell-cell binding and the interactions between cells and extracellular matrix (ECM) proteins. They may also trigger intracellular pathways and participate in cellular processes such as migration, proliferation, differentiation, and cell death. Presently, four major classes of adhesion receptors have been described: the immunoglobulin superfamily, cadherins, integrins, and selectins. The development of multicellular organs requires adhesion structures to ensure adequate communication between constituent cells and the anchorage of cells to the extracellular matrix. The availability of electron microscopy has made possible the study of highly specialized cell-cell contact structures. These structures include occludens-type connections or tight junctions, adherens-type connections, including desmosomes and adhesion plaques, and gap junctions.

Recently, the molecular elements that form these microscopic adhesion structures have been described. The junctional structures consist of transmembrane elements (adhesion receptors) associated with several cytoplasmic molecules that are linked to cytoskeletal filaments. Although the biologic functions of several families of adhesion molecules are well-known, current research is predominantly focused on identifying their ligands, the signal pathways associated with them, and their therapeutic potential.

In the discussion that follows, the structure and function of some of the most important adhesion receptors in epithelial tissues are reviewed. Their roles in cell development, epithelial adhesion, leukocyte functions, apoptosis, and neoplasia will be presented. This review is not intended to be all-inclusive or extensive in its coverage. Our purpose is to familiarize the reader with emerging information that has many potentials for future clinical applications. Many of the examples used are not from studies of epidermal cells, but from cells of other organs. This was done to demonstrate specific functions of adhesion receptors that eventually may or may not apply to the oral mucosa. Similarly, several observations derived from tissue culture experiments and animal models have been included, even though their direct application to humans is not clearly understood. They have been included in this discussion merely to demonstrate the biologic diversity and extensive function of the adhesion receptors.

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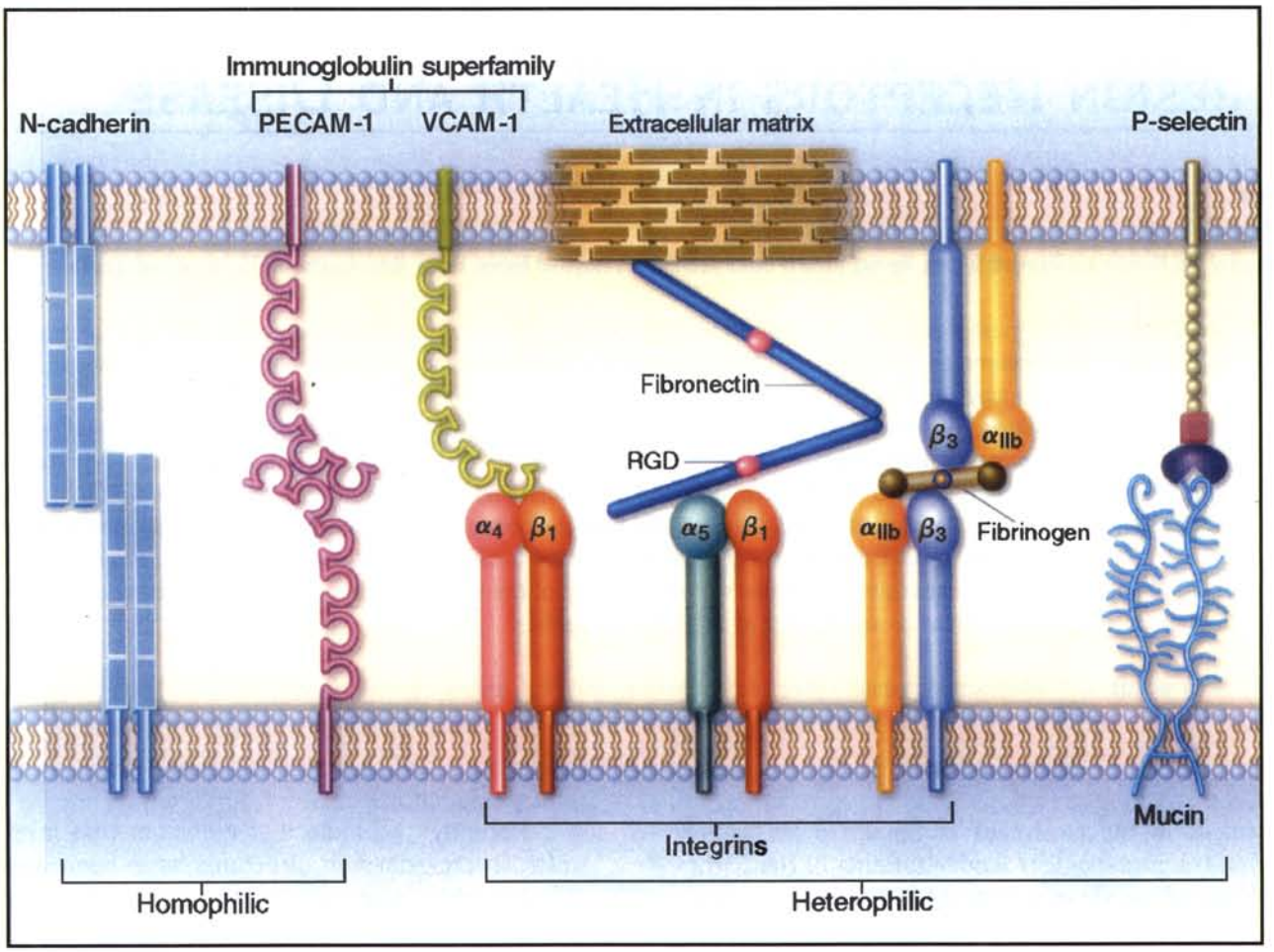

Figure 1. The four major classes of adhesion receptors, shown embedded in a putative plasma membrane. Cadherins typically mediate a calcium-dependent, homophilic adhesion between cells. The crystal structure of the domains of these receptors suggests that adjacent molecules form dimers and interact with dimers on the opposite cell. N-cadherin is one of the adhesion molecules mediating the outgrowth of neurites. The second major class, the immunoglobulin superfamily, may also mediate homophilic interactions. The binding sites of these receptors are characteristically, but not always, in the two most distal domains. They mediate cell-cell adhesion that is not dependent on divalent cations. Platelet-endothelial-cell adhesion molecule (PECAM-1), also expressed on leukocytes, appears to have a role in the migration of leukocytes across the endothelium. Other members of the immunoglobulin superfamily mediate heterophilic interactions with integrins. For example, the vascular-cell adhesion molecule 1 (VCAM-1), found on stimulated endothelial cells, binds the α4b1 or α4b7 integrin on lymphocytes. Integrins, the third major class, are heterodimers whose two chains contribute to ligand binding, which requires the presence of divalent cations. Many integrins bind to proteins in the extracellular matrix, as shown with $\alpha5\beta1$, which is a receptor for fibronectin and can support the assembly of the fibronectin matrix. Integrins also bind soluble adhesion molecules, such as fibrinogen, which forms cross-links with the platelet integrin αIIbβ3 during platelet aggregation. A short motif in the amino acid sequence, such as arginine-glycine-aspartic acid (RGD), is often the primary site of recognition by the integrin receptor. Finally, the selectins, which have a distal calcium-dependent lectin domain, interact with carbohydrate groups on highly glycosylated protein ligands. P-selectin is found on activated platelets and endothelial cells and mediates adhesion to specific mucins present on many leukocytes. (From Frenette and Wagner, 1996; all rights reserved.)

Classification of Adhesion Receptors

IMMUNOGLOBULIN SUPERFAMILY

Several members of the immunoglobulin family are involved in cellular adhesion (Williams and Barclay, 1988). These cell-surface proteins consist of a variable number of extracellular Ig-like domains with conserved cystein sequences, a transmembrane region, and a cytoplasmic region. The latter region has been shown to bind to the cytoskeleton (Carpen *et al.*, 1992). The members of this family include the platelet-endothelial-cell adhesion molecule (PECAM-1), the neural-cell adhesion molecule (N-CAM), the vascular-cell adhesion molecule (VCAM-1), the intracellular adhesion molecules (ICAM-1, ICAM-2, ICAM-3), and the mucosal addressin (MAdCAM) (Buck, 1992; Briskin *et al.*, 1993) (Table 1). PECAM-1 is present in

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circulating platelets, monocytes, neutrophils, and selected T-cell subsets. It is also a major constituent of the intercellular junction of the endothelium and is associated with the migration of the leukocytes across the vessel wall (Liao *et al.*, 1995; Berman *et al.*, 1996; Christofidou-Solomidou *et al.*, 1997) (Fig. 1). N-CAM is present on the surfaces of nerve and glia cells and activates second-messenger cascades that promote nerve growth (Williams *et al.*, 1994; Doherty and Walsh, 1996). It is also expressed during molar tooth development in the mouse (Obara and Takeda, 1993). VCAM-1 is found in activated endothelial cells and is related to the leukocyte adhesion phenomenon by binding with integrin molecules expressed in lymphocytes (Fries *et al.*, 1993) (Fig. 1). ICAM-1 is expressed at low levels on leukocytes, fibroblasts, and epithelial and endothelial cells. ICAM-1 is upregulated by cytokine and inflammatory mediators and is associated with leukocyte recruitment during inflammatory and immune responses (Kirchhausen *et al.*, 1993; Crawford and Watanabe, 1994; Hayashi *et al.*, 1994; Canonica *et al.*, 1995). ICAM-2 is present at high levels on the endothelium and is involved in the leukocyte adherence mechanism (Crawford and Watanabe, 1994; Xu *et al.*, 1996). ICAM-3 is expressed on resting leukocytes and vascular endothelium of some tumor vessels (Acevedo *et al.*, 1993). ICAM-3 is involved in the initiation of immune responses, and it is suggested that this molecule may play a role in angiogenesis and tumor development (Starling *et al.*, 1995; Patey *et al.*, 1996). MAdCAM is found in Peyer's patches and mesenteric lymph nodes. MAdCAM binds to L-selectin to facilitate the adherence of leukocytes to the endothelium (Berg *et al.*, 1993).

TABLE 1

Immunoglobulin Superfamily Adhesion Receptor Distribution and Ligands

Ig-like Molecule	Ligands	Distribution
ICAM-1	αLβ2, αMβ2	Some lymphocytes, macrophages, activated fibroblasts and epithelium
ICAM-2	αLβ2	Endothelial cells, lymphocytes, monocytes
ICAM-3	αLβ2, αdβ2	Resting leukocytes, hematopoietic cells, vessels of malignant tumors
MAdCAM-1	L-selectin, α4β7	Mesenteric lymph nodes, Peyer's patches
PECAM-1	αVβ3, PECAM-1	Platelets, monocytes, neutrophils, selected T-cell subsets
VCAM-1	α4β7, α4β1, CLA	Activated endothelial cells

Abbreviations: ICAM, intracellular adhesion molecule; MAdCAM, mucosal addressin; PECAM, platelet-endothelial-cell adhesion molecule; VCAM, vascular-cell adhesion molecule; CLA, cutaneous lymphocyte antigen.

CADHERINS

Cadherins are a group of membrane proteins with a molecular weight of approximately 130 kDa. Cadherins can be grouped into classic cadherins, desmosomal cadherins, and protocadherins (Sano *et al.*, 1993; Tanihara *et al.*, 1994a,b). Some of the members of each group and their localization are shown in Table 2. The classic cadherins are membrane proteins composed of three regions: an extracellular N-terminal domain, a transmembrane sequence, and a conserved C-terminal cytoplasmic region (Takeichi *et al.*, 1988). The extracellular region consists of five structurally homologous segments containing calcium-binding motifs. Cadherins form zipper-like structures through homophilic interactions between adjacent molecules (Shapiro *et al.*, 1995) (Fig. 1). An anchoring domain and a cadherin-typical domain characterize the intracellular region. The latter domain has a highly conserved amino acid sequence with a carboxylic terminal end. It has been shown that the activity of the cadherins depends on the interaction between this cytoplasmic domain and different cytoplasmic proteins (*i.e.*, α, β, and γ catenins, plakoglobin, and p120) (Kemler, 1993; Nagafuchi *et al.*, 1993; Reynolds *et al.*, 1994). The α-catenins and plakoglobin

TABLE 2

Cadherin Localization and Ligands

Cadherin Type	Ligands	Localization
Classic		
E-cadherin	E-cadherin, aEb7	Zonula adherens
P-cadherin	P-cadherin	Zonula adherens
N-cadherin	N-cadherin	Zonula adherens
Desmosomal cadherins		
Dcs 1	HB	DS mostly SSE
Dcs 2	HB	All desmosomes bearing tissues
Dgls 1	HB	Desmosomes mostly SE
Dgls 2	HB	All desmosomes bearing tissues
Dgls 3	HB	Desmosomes mostly SE
Protocadherins	Unknown	Central nervous system

Abbreviations: DS, desmosomes; SSE, stratified squamous epithelium; SE, stratified epithelium; HB, homophilic binding; Dcs, desmocollins; Dgls, desmogleins.

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TABLE 3

Selectin Distribution and Ligands

Selectins	Ligands	Distribution
L-selectin	GlyCAM-1, sLe^x, CD34, PSGL-1, MAdCAM-1	Lymphocytes, monocytes, neutrophils
E-selectin	CLA, sLe^x	Activated endothelial cells
P-selectin	PSGL-1, sLe^x	Platelets, endothelial cells

Abbreviations: MAdCAM, mucosal addressin; PECAM, platelet-endothelial-cell adhesion molecule; VCAM, vascular-cell adhesion molecule; sLex, sialylated Lewis X; GlyCAM, glycosylation-dependent cell adhesion molecule.

show an amino acid sequence resembling that of another cytoplasmic protein called vinculin, which mediates the linkage of the cadherin-catenin complex to the cytoskeleton (McCrea *et al.*, 1991). Plakoglobin is highly homogeneous with γ-catenin (Peifer *et al.*, 1992). β-catenins and plakoglobin can also act as signaling molecules, translocate to the nucleus, bind transcription factors, and control gene expression (Huber *et al.*, 1996; Larue *et al.*, 1996).

SELECTINS

The selectins are carbohydrate-binding glycoproteins that contain 5 different domains: three extracellular, one transmembrane, and one intracellular. The extracellular domains consist of an amino terminal carbohydrate-recognition domain, an epidermal growth factor-like (EGF-like) motif, and a sequence of short consensus repeat units (SCR) (Siegelman *et al.*, 1989; Lasky, 1991). The intracellular domain is characterized by a short carboxyl terminal tail (Johnston *et al.*, 1989). The integrity of the EGF-like domain and the SCR domain is necessary for the ligand-receptor affinity and for the cell adhesion properties of selectins (Kansas *et al.*, 1994). Among selectins, P-selectins are found on activated platelets and endothelial cells. P-selectins mediate adhesion to specific glycoproteins on leukocytes. L-selectins are found in leukocytes and mediate the homing of lymphocytes to the lymph nodes. E-selectins are expressed by endothelial cells after cytokine activation and participate in vascular leukocyte rolling (Bevilacqua *et al.*, 1991) (Table 3). Recently, it has been demonstrated that E-selectins are also expressed in human gingival epithelial tissue on both keratinocytes and endothelial cells (Pietrzak *et al.*, 1996a,b).

The selectins are important for leukocyte-endothelium interactions and inflammatory responses. Peripheral blood leukocytes bind to selectins that are expressed by activated endothelium (Lasky, 1991; Dore *et al.*, 1993; Ley *et al.*, 1995).

INTEGRINS

Integrins consist of a family of several transmembrane glycoproteins that are important for the interaction between cells and the extracellular matrix. The integrins are heterodimers composed of two subunits, α and β, that are non-covalently combined. Eight α subunits and 15 β subunits have been identified, and the various combinations of α and β subunits constitute at least 20 different integrin molecules (Hynes, 1992) (Table 4). Integrin subunits may associate to form at least 100 integrin heterodimers, but in fact, their associations are restricted. Some α subunits associate only with a specific β subunit. For instance, white blood cells express β1, β2, and many α subunits. β1 can form heterodimers with α1, α2, α3, α4, α5, α6, α7, α8, and α9, while β2 associates only with αX, αM, αL, and αd integrins. However, few α subunits (α4, α6, and αV) can associate with more than one β subunit (Nicolas and Staquet, 1995).

Integrins are located on the cell membrane and differ in their ligand-binding specificities. Each subunit contains a large extracellular domain, a transmembrane segment, and a short cytoplasmic domain (Fig. 1). The molecular size of the α subunit varies between 120 and 180 kDa, while β subunits vary from 85 to 110 kDa, with the exception of the β4 subunit, which has a size of 205 kDa (Tamura *et al.*, 1990). The cytoplasmic domain forms links with the cytoskeleton and controls the ligand-binding affinity of the extracellular domain (Hughes *et al.*, 1995). The extracellular domain of both subunits interacts with ECM proteins and other ligands (*e.g.*, bacterial proteins, coagulation factors, viral proteins, and other adhesion molecules) (Coburn *et al.*, 1993; Wayner *et al.*, 1993; Wickham *et al.*, 1993; Palecanda *et al.*, 1997).

The integrin-ligand interaction produces two signaling events in the cell. An "outside-in" signaling event is characterized by the triggering of intracellular pathways (frequently by tyrosine phosphorylation of various intracellular proteins) that may alter different processes such as gene regulation, proliferation, and programmed cell death. For example, when synovial fibroblasts are placed on surfaces coated with fragments of fibronectin, or antibodies against the α5β1 integrin, a significant induction of metalloproteinase expression is observed (Huhtala *et al.*, 1995). Another study has shown that normal epithelial cells placed in the absence of ECM proteins entered into apoptosis (Frisch and Francis, 1994). Another integrin-ligand interaction is the trans-dominant inhibition, in which the occupancy of one integrin receptor can suppress the function of another integrin (Diaz-Gonzalez *et al.*, 1996; Huang *et al.*, 1996). A second integrin signaling mechanism, which is referred to as

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TABLE 4

Integrin Localization and Ligands

Integrins	Ligands	Localization
α1β1	Collagen I and IV (laminin)	Activated lymphocytes, endothelium, hepatocytes
α2β1	Collagen I and IV (laminin) α3β1, tenascin, echovirus	Epithelium, endotheliun, leucocytes, platelets, basal keratinocytes, melanoma cells
α3β1	Fibronectin, laminin (5,1), collagen I, epiligrin, entactin, thrombospondin	Epithelium, endothelium, basal keratinocytes
α4β1	Fibronectin, VCAM-1, CLA	Tumor cells, muscle, leucocytes
α5β1	Fibronectin	Fibroblasts, platelets, lymphocytes, hepatocytes, basal keratinocytes, chondrocyte, Tat protein
α6β1	Laminin	Epithelium, endothelium, mast cells, platelets, leukocytes, tumor cells
α7β1	Laminin	Melanoma cells, muscle cells
α8β1	Vitronectin, fibronectin, tenascin, vWF	Epithelium, endothelium, brain cells
α9β1	Tenascin, vWF	Basal keratinocytes, squamous epithelium
αVβ1	Vitronectin, fibronectin	Epithelium
αLβ2	Fibrinogen, C3bi, telencephalin, CLA	Leucocytes
αMβ2	Fibrinogen, C3bi, Factor X, ICAM-1 ICAM-2, elastase, kininogen	Leukocytes, macrophages
αDβ2	ICAM-3	Lymphocytes, macrophages, intestinal mucosa
αXβ2	Fibrinogen, C3bi	Leukocytes, macrophages
αIIββ3	Fibrinogen, vWF, thrombospondin *Borrelia burgdorferi*	Platelets
αVβ3	Fibrinogen, vWF, fibronectin, PECAM-1 bone sialoprotein, vitronectin, adenovirus	Fibroblasts, osteoblasts, glial cells, endothelium, endometrium, melanoma cells, platelets, kidney
α6β4	Laminin (1,5)	Epithelium, fibroblasts, neurons, Schwann cells
αVβ5	Vitronectin, adenovirus	Fibroblasts, epithelium, tumor cells
αVβ6	Fibronectin, tenascin	Epithelium, tumor cells
α4β7	MAdCAM-1, VCAM-1, FN	Activated lymphocytes, eosinophils, mast cells
αVβ8	Unknown	Kidney, brain, ovary, uterus, placenta

Abbreviations: vWF, von Willebrand factor; CLA, cutaneous lymphocyte antigen; MAdCAM, mucosal addressin; PECAM, platelet-endothelial-cell adhesion molecule; VCAM, vascular adhesion molecule; ICAM, intracellular adhesion molecule.

"inside out", occurs when an activated cell sends a signal through the cytoplasmic domain of the integrin to change the extracellular domain conformation. This action may affect the integrin-ligand affinity positively or negatively (Shimizu *et al.*, 1990; Ginsberg *et al.*, 1992; O'Toole *et al*, 1994; Diaz-Gonzalez *et al*, 1996).

The integrin heterodimers present in the normal epidermis are α2β1, α3β1, α5β1, and α6β4 (Watt and Hertle, 1994). α6β4 is predominantly expressed in the basal pole of the basal keratinocyte and is part of the hemidesmosome, a structure that participates in the adhesion of the keratinocytes to the basement membrane (Dowling *et al.*, 1996; Georges-Labouesse *et al.*, 1996b; Van der Neut *et al.*, 1996). α2β1 and α3β1 are expressed on the lateral and apical surfaces of basal keratinocytes and in lesser amounts in the keratinocyte basal pole. It is believed that they are involved in keratinocyte cell-cell adhesion (Watt and Jones, 1993). In wounded epidermis, the expression of integrins is altered such that they can be found in suprabasal cells (Gailit *et al.*, 1994). Keratinocytes at the wound margin begin migrating over the wound bed soon after injury. These keratinocytes express high levels of α5β1 and αVβ5 (Watt and Jones, 1993; Gailit *et al.*, 1994; Watt and Hertle, 1994). The induction of these integrins in migrating keratinocytes may facilitate the migration, because these integrins are receptors for protein ligands, present in the clot provisional matrix, such as fibronectin or vitronectin (Cavani *et al.*, 1993). The expression of integrin receptors by human keratinocytes during wound healing may be a response to cytokines present in the clot matrix. Recent studies suggest that during wound repair, TGF-beta 1 may induce epidermal keratinocytes to express integrins that facilitate the migratory component of re-epithelialization (Gailit *et al.*, 1994).

Counterreceptors and Ligands

Several integrin ligands have been described: ECM proteins (fibronectin, collagens, laminin), molecules of the immunoglobulin superfamily (VCAM-1, MAdCAM-1), coagulation factors (von Willebrand factor, Factor X), fib-

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rinolytic factors (Fibrinogen, Fibronectin), and the complement factor C3b. In addition, some bacterial and viral proteins have also been found to interact with integrins (Table 4). For instance, a protein of the Lyme disease spirochete, *Borrelia burgdorferi*, binds to platelets through the αIIbβ3 integrin. This binding facilitates the spirochete's dissemination throughout the body (Coburn *et al.*, 1993). The adhesion of adenovirus 2 to host cells is facilitated by the binding of viral proteins to the αMβ2 integrin. Its entry into the host cell is promoted by the binding of viral proteins to αVβ3 and αVβ5 integrins (Wickham *et al.*, 1993; Huang *et al.*, 1996). Integrins commonly recognize short linear sequences of amino acids, such as Arg-Gly-Asp (RGD) (Pierschbacher and Ruoslahti, 1984), which are present in extended loops of the β turns (Main *et al.*, 1992; Tomiyama *et al.*, 1992). Many studies suggest that this secondary conformation is crucial for ligand recognition by the integrin (Dickinson *et al.*, 1994; Krezel *et al.*, 1994). RGD sequences are present in many ligands, such as the Tat protein of the HIV type 1. The Tat protein acts as a growth factor for the AIDS Kaposi sarcoma cells and supports the adhesion mechanisms of these cells through the integrin receptors α5β1 and αVβ3 (Barillari *et al.*, 1993). Although the interaction between the Tat protein and α5β1 and αVβ3 receptors is well-known, the pathogenic implications of this binding are still under investigation. Recently, it was suggested that the binding of the Tat protein with α3 and α5 integrins activates quiescent T-cells. This phenomenon renders T-cells more susceptible to infection by HIV-1 (Li *et al.*, 1997).

Some integrins recognize only one ligand (*e.g.*, α5β1 binds to fibronectin), whereas others bind several ligands (*e.g.*, α3β1 binds to laminin, collagen IV, and fibronectin). Different domains of a protein can bind to distinct integrins and activate different biologic functions. The ligation of the G2 domain of entactin, a basement membrane protein, with α3β1 integrin on neutrophils stimulates Fc receptor-mediated phagocytosis. Furthermore, the interaction of the E domain of entactin with the β3-like integrin on neutrophils activates neutrophil chemotaxis (Gresham *et al.*, 1996). Fibronectin has the RGD sequence and also 3 other binding sites, recognized by different integrins. Lys-Gln-Ala-Gly-Asp-Val (KQAGDV) binds to αIIbβ3 integrins on platelets and mediates platelet aggregation. Glu-Ile-Leu-Asp-Val (EILDV) and Ile-Asp-Ala-Pro-Ser (IDAPS) bind to α4β1 and mediate cell adhesion (Mohri, 1996).

Some other integrins also bind to receptors of the immunoglobulin family, such as ICAM-1 and VCAM-1. ICAM-1 interacts with β2 integrins on leukocytes to initiate many leukocyte immunologic functions. VCAM-1 and MAdCAM-1 interact with α4 integrins expressed by rat mast cell lines. These interactions may regulate the accumulation of mast cells at inflammatory sites in many tissues and in Peyer's patches in the gut (Palecanda *et al.*, 1997). ICAM-1 is also a receptor for pathogens like rhinovirus. Rhinovirus, binding to ICAM-1 molecules of the conjunctiva and nasal epithelium, facilitates rhinovirus infection (Rossmann, 1994). In malaria, it has been observed that the *Plasmodium falciparum*-infected erythrocytes bind to ICAM-1 receptors expressed on the endothelium (Gardner *et al.*, 1996). Animal studies suggest that this attachment is the cause of the cerebral microvessel thrombosis that is observed in cerebral malaria. Recently, it was found that, in a *Plasmodium coatneyi*-infected rhesus monkey, the sequestration of parasitized red blood cells was also the result of the attachment of these cells to ICAM-1 and other cyto-adhesion molecules expressed in the endothelium of microvessels present in several organs (Smith *et al.*, 1996).

The ligands for selectins are generally mucin-like molecules (Table 3). Most of them present serine/threonine-rich regions that are substituted with O-linked carbohydrate chains (Shimizu and Shaw, 1993). The most studied selectin ligands are CD34, the glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1), mucosal addressin (MAdCAM-1), sialylated Lewis X (sLe^x), and P-selectin glycoprotein ligand (PSGL-1). CD34 is a mucin-like polypeptide expressed by vascular endothelial cells (Baumhueter *et al.*, 1994). GlyCAM-1 is a small mucin-type glycoprotein that is expressed by endothelial cells present in post-capillary venules of lymph nodes and inflamed tissues (Imai *et al.*, 1992; Hemmerich *et al.*, 1994). MAdCAM-1 is an endothelial adhesion protein of the immunoglobulin family found in the Peyer's patch and mesenteric lymph nodes (Berg *et al.*, 1993). MAdCAM-1 and GlyCAM-1 are also ligands for molecules of the integrin family (Erle *et al.*, 1994). sLe^x is a fucosylated carbohydrate structure that is recognized by L-selectins, P-selectins, and E-selectins. Modifications of this structure are commonly seen in other selectin ligands (Foxall *et al.*, 1992).

PSGL-1 is expressed by circulating neutrophils, monocytes, and CD34+ hematopoietic progenitor cells. This molecule mediates neutrophil rolling on P-selectins and E-selectins (Sako *et al.*, 1993). PSLGL-1 can also interact with L-selectins to mediate neutrophil rolling over adherent neutrophils and promote continuous leukocyte recruitment (Spertini *et al.*, 1996). Another selectin ligand is the cutaneous lymphocyte antigen (CLA). CLA is a specialized form of PSGL-1 that serves as an E-selectin and P-selectin ligand on a subpopulation of memory/effector T-cells (Fuhlbrigge *et al.*, 1997). CLA+ cells comprise the majority of T-cells found at sites of cutaneous inflammation in humans. E-selectins are also expressed on venules at these inflamed sites, suggesting that E-selectins and CLA serve as a receptor-ligand pair in the homing of the T-cells to the skin (Rossiter *et al.*, 1994).

In order to interact with selectins, ligands need to be modified. Ligands may be modified by being glycosylat-

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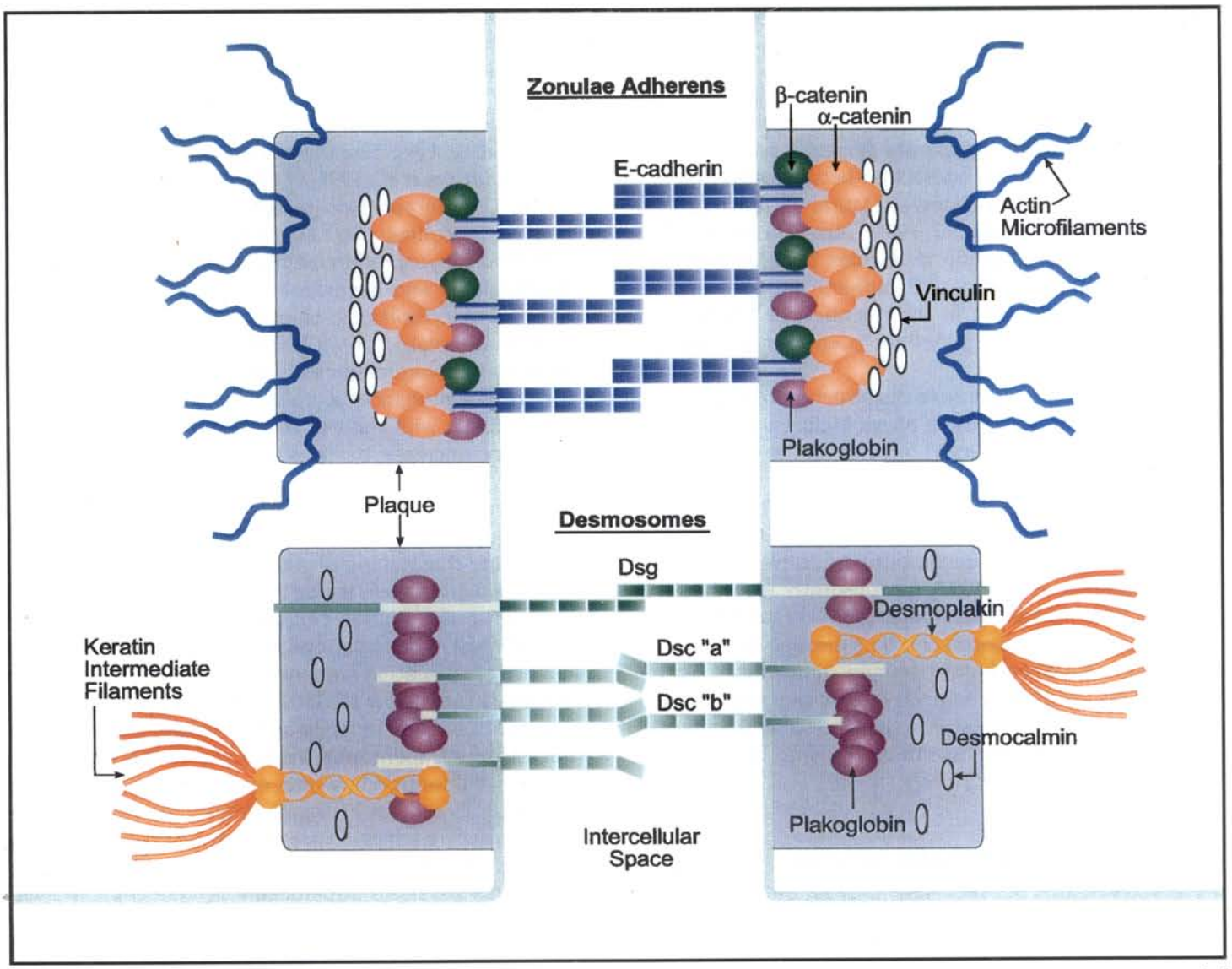

Figure 2. Model of the structure of the desmosomes (DS) and zonulae adherens (ZA) interconnecting keratinocytes. ZA is composed of classic cadherins (E-cadherin) that mediate homotypic cell-cell adhesion. The suggested binding sites of cadherins are the two most distal domains. The cytoplasmic portion of the E-cadherin forms complexes with either the β-catenin or plakoglobin. Either one is associated with α-catenin, which is also associated with the actin microfilament network (AMN) (McCrea *et al.*, 1991; Sacco *et al.*, 1995). Vinculin is a protein characteristic of the ZA, that links the cadherin-catenin complex to the AMN (Haftek *et al.*, 1996). DS have two transmembrane components, desmocollins (Dcs) and desmogleins (Dsg). DS also have plaque proteins such as desmoplakin and plakoglobin. The cytoplasmic portions of the Dcs are alternatively spliced, which results in two cytoplasmic domains of different sizes: the longer "a" form and the shorter "b" form (Buxton and Magee, 1992; Amagai, 1995). Both Dcs and Dsg bind to plakoglobin at the cytoplasmic plaque. Desmoplakin has a rod-like structure unique to DS and is located between the plaque and the intermediate filaments. The "a" form of Dcs binds to the NH2-terminal region of desmoplakin; the desmoplakin COOH-terminal end binds to the keratin intermediate filaments (Kouklis *et al.*, 1994; Amagai, 1995). Desmocalmin is a protein that may participate in the anchorage of keratin intermediate filaments (Burge, 1994).

ed, sulfated, or fucosylated (Varki, 1997). In the case of CLA, investigators propose that this molecule is the result of post-translational modification of the PSGL-1, mediated by fucosyltransferase VII (Fuhlbrigge *et al.*, 1997). The absence of ligands for selectins may play a role in the pathogenesis of some diseases. For instance, in the leukocyte adhesion deficiency type II syndrome, which is characterized by developmental abnormalities, leukocytosis, and recurrent infections, the synthesis of sLeX is impaired. Therefore, the leukocytes of these patients are unable to migrate and reach the sites of infection (Etzioni *et al.*, 1992, 1993; von Andrian *et al.*, 1993). Other ligands for selectins such as heparin sulfate glycosaminoglycans and the mucin-like glycoproteins

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expressed by carcinomas are presently being studied (Norgard-Sumnicht and Varki, 1995; Kim *et al.*, 1996; Giuffre *et al.*, 1997).

Classic cadherins prefer to interact homophilically. It has been found that two cell populations expressing two different cadherins form separate aggregates when they are mixed. However, the interaction between two different cadherins has been observed (Murphy-Erdosh *et al.*, 1995; Nakagawa and Takeichi, 1995). Interactions of cadherins with other adhesion molecules have also been described. The association of E-cadherin with the αEβ7 integrin may have a role in the retention of T-lymphocytes in the mucosal epithelium (Cepek *et al.*, 1994; Karecla *et al.*, 1995).

Compounds that resemble the structure of adhesion molecule ligands constitute a physiological way to treat diseases. The binding of αVβ3 integrin on the osteoclast surface to its ligand, osteopontin, may prevent bone resorption (Reinholt *et al.*, 1990; Ross *et al.*, 1993). Loss of this binding may be a possible mechanism that could induce or trigger bone resorption. In cultured osteoclasts, Engleman *et al.* (1997) have recently identified a synthetic RGD mimetic peptide (SC56631) that binds to the αVβ3 osteoclast integrin and thus prevents bone loss in rats. As mentioned before, human rhinoviruses bind with ICAM-1 to infect conjunctiva and the respiratory epithelium. Studies have shown that the soluble form of ICAM-1 may be effective in inhibiting virus binding to host cells (Huguenel *et al.*, 1997).

Role in Epithelial Adhesion

Stable connections between cells play an essential role in overall tissue organization and function. Several adhesive structures are present in epithelial cells, including desmosomes (DS), hemidesmosomes (HDS), and zonula adherens (ZA). In the ZA, there are many cell junction proteins (Fig. 2). The adhesion receptors present at the ZA are classic cadherins. In the epithelium, the ZA adhesion receptor is E-cadherin. The continued expression and functional activity of E-cadherins are required for cells to remain tightly associated in the epithelium. In order to exhibit their adhesion activity, cadherins must form complexes with catenins, which are linked to actin microfilaments (Kaiser *et al.*, 1993). α-catenins, plakoglobin (γ-catenin), β-catenins, and vinculin are cytoplasmic plaque proteins (Kaiser *et al.*, 1993; Haftek *et al.*, 1996). Vinculin is a plaque protein characteristic of the ZA. Recent research has shown that plakoglobin, previously associated with both DS and ZA, is localized only at DS structures (Haftek *et al.*, 1996). The role of ZA in the epidermis is unclear. It is suggested that the ZA is essential in the control of keratinocyte stratification and participates in DS morphogenesis (Lewis *et al.*, 1994; Haftek *et al.*, 1996). The ZA is also important for the maintenance of normal tissue conformation. A loss of E-cadherin expression or function leads to enhanced cell invasiveness in cell culture and is correlated with aggressive behavior and metastasis of certain human tumors (Frixen *et al.*, 1991; Shimoyama *et al.*, 1992; Shiozaki *et al.*, 1996; Andrews *et al.*, 1997; H Chen *et al.*, 1997).

In DS, the adhesion receptors are the desmogleins and desmocollins (Fig. 2). These receptors are transmembrane glycoprotein members of the cadherin family. Desmogleins and desmocollins are linked to a keratin network by cytoplasmic plaque proteins, called desmoplakins and plakoglobin (Buxton and Magee, 1992). This desmosomal-intermediate filament system is essential for the maintenance of epidermal tissue integrity. DS interconnect with individual keratin cytoskeleton structures and increase tissue resistance to shearing forces (Stanley, 1995).

Several autoimmune blistering diseases result from the disruption of DS (Stanley, 1995). Pemphigus vulgaris (PV), a life-threatening blistering disease of the skin and mucous membranes, is due to the loss of cell-cell adhesion in the supra-basalar epidermis (Shimizu *et al.*, 1995). The clinical manifestations of PV are a direct consequence of circulating autoantibodies against desmoglein 3 (Dsg-3) (Amagai *et al.*, 1992, 1996; Karpati *et al.*, 1993). The clinical characteristics of the disease can be reproduced by intraperitoneal injections of the pemphigus vulgaris autoantibodies into neonatal mice (Amagai *et al.*, 1992). PV-similar histopathological features and loss of keratinocyte adhesion are observed in Dsg-3 null mice (Koch *et al.*, 1997). In pemphigus foliaceus, the adhesion defect occurs more superficially at the granular layer (Shimizu *et al.*, 1995). It is caused by autoantibodies against desmoglein-1 (Dsg-1) (Amagai *et al.*, 1995).

HDS are basement membrane attachment structures that form dense cytoplasmic plaques at the basal pole of the keratinocyte. HDS are linked intracellularly to the keratin filament network and extracellularly to the basement membrane (Schwarz *et al.*, 1990). These junctions contain α6β4 integrin heterodimers, the Bullous Pemphigoid Antigen-1 (BPAG-1), and BPAG-2. The α6β4 integrin is linked to laminin-5 and laminin-1 filaments in the basement membrane (Fig. 3) (Sonnenberg *et al.*, 1991; Nissen *et al.*, 1994). BPAG-1 is a 230-kDa protein that shows a sequence homology with desmoplakin and is localized in the cytoplasm of basal keratinocytes at the level of the HDS (Sawamura *et al.*, 1991; Thatcher *et al.*, 1991). BPAG-2, also known as type XVII collagen, is a transmembrane protein with a molecular weight of 180 kDa (Hirako *et al.*, 1996). BPAG-2 is formed by an extracellular domain, a transmembrane domain, and an intracellular domain. It is believed that the extracellular domain binds to proteins of the lamina lucida and pro-

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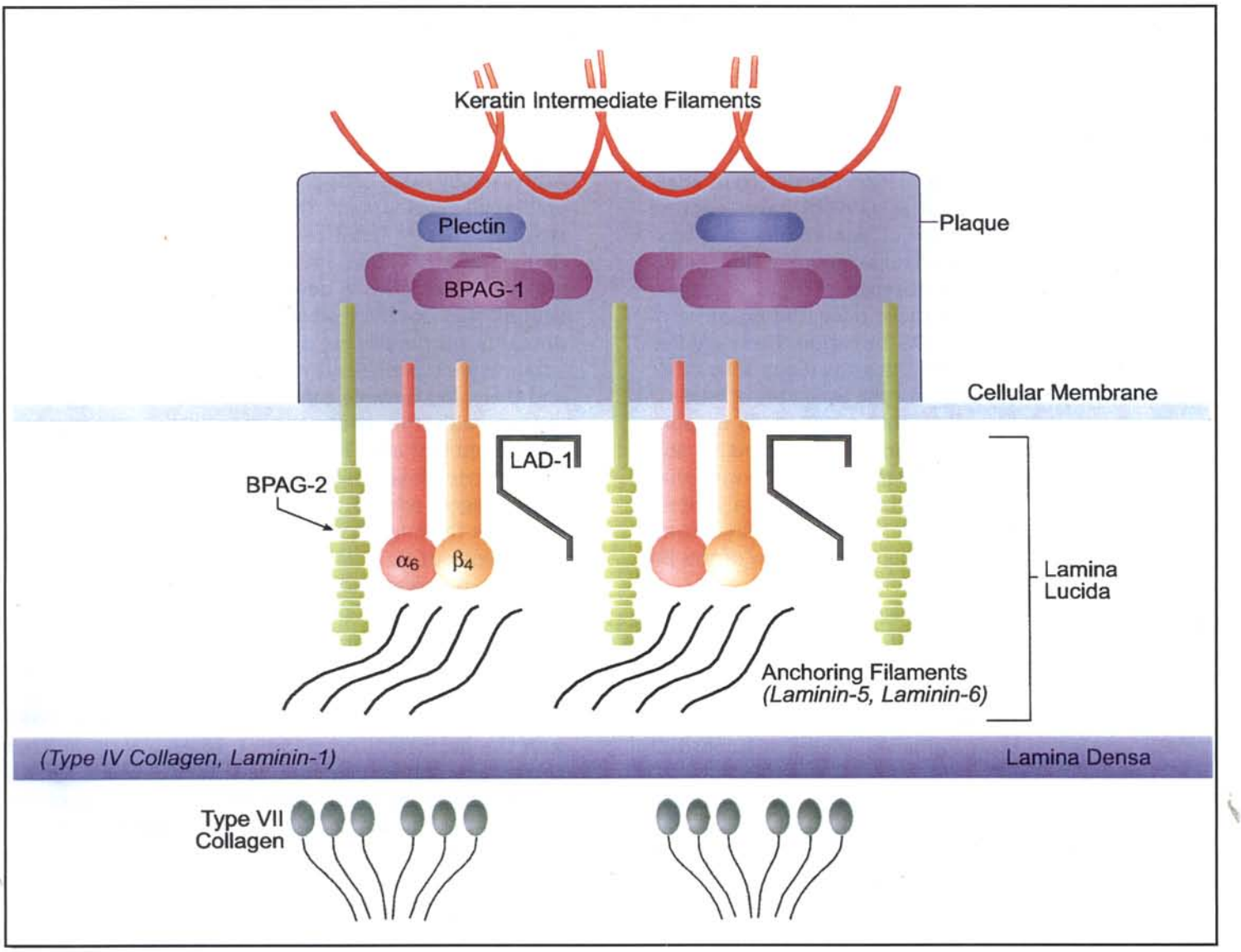

Figure 3. Model of the structure of the hemidesmosomes at the basal pole of keratinocytes. The proteins that are known to constitute the hemidesmosomes (HDS) are the a6b4 integrin, BPAG-1, and BPAG-2. BPAG-1 is located inside the electron-dense plaque of the HDS. BPAG-1 has a structure similar to that of plectin and desmoplakin and, like these proteins, binds to the keratin intermediate filament network (Sawamura *et al.*, 1991; Thatcher *et al.*, 1991). BPAG-2 and the $\alpha 6\beta 4$ integrin are transmembrane elements whose extracellular domains are localized at the lamina lucida of the basal membrane. Anchoring filaments (AF) are fibrils formed by laminin-5 (also called epiligrin, kalinin, or nicein), laminin-6, and may also include the antigen of the Linear IgA Bullous Disease (LAD-1) (Ishiko *et al.*, 1996). It is suggested that the AF extend from the HDS to the lamina densa. The $\alpha 6\beta 4$ integrin mediates basal keratinocyte cell adhesion by binding laminin-5 and laminin-1 at the lamina lucida (Sonnenberg *et al.*, 1991; Nissen *et al.*, 1994).

motes adhesion of basal keratinocytes to the epidermal basement membrane. Patients with bullous pemphigoid, a blistering disease that occasionally involves oral mucosa, have circulating antibodies against BPAG-1 and BPAG-2 (Sawamura *et al.*, 1991; Giudice *et al.*, 1992). The binding of antibodies to BPAG-1 and BPAG-2 may precipitate the development of blisters in these patients.

Alterations in the BPAG-1 and BPAG-2 are also associated with Junctional Epidermolysis Bullosa (JEB). This disease is characterized by blister formation at the dermo-epidermal junction and recurrent erosions in the gastrointestinal, genito-urinary, and respiratory tracts and the cornea. Laminin-5, a component of the basal membrane, may play a role in the physiopathology of the JEB. In patients with JEB, antibodies against laminin-5 or mutations on the gene encoding laminin-5 have been reported (Schofield *et al.*, 1990; Gil *et al.*, 1994; Pulkkinen *et al.*, 1994; McGrath *et al.*, 1996). Patients with JEB and pyloric atresia (JEB/PA) present similar clinical characteristics but fail to show abnormalities in laminin-5 (Brown

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et al., 1996). Studies in JEB/PA patients have found a weak anti-β4 integrin labeling and homozygous mutations of the β4 and α6 integrin genes (Phillips *et al.*, 1994; Vidal *et al.*, 1995; Pulkkinen *et al.*, 1997). Studies using β4 integrin knockout mice showed separation of the dermo-epidermal junction, absence of HDS, and substantial loss of cell adhesion (Dowling *et al.*, 1996; Van der Neut *et al.*, 1996). Georges-Labouesse *et al.* (1996b) have reported that α6 integrin null mice die of skin and mucosa blistering. These animals showed detachment of the epidermis from the dermis and absence of HDS (Georges-Labouesse *et al.*, 1996b). In these mice, the presence of β4 alone is not enough for HDS formation. These studies suggest that both α6 and β4 integrins along with other molecules may be necessary for the assembly of HDS.

Ocular cicatricial pemphigoid (OCP) is an autoimmune disease that affects mainly the conjunctiva and other squamous epithelia. Recently, it was reported that the autoantibody in OCP binds to a 205-kDa protein (Tyagi *et al.*, 1996). Interestingly, this antigen has a complete homology with the cytoplasmic domain of the β4 integrin (Tyagi *et al.*, 1996).

A recent investigation also suggests that a structural variant of the human α6 integrin is probably involved in the pathogenesis of oral pemphigoid (OP) (Bhol *et al.*, 1997). Autoantibodies from OP patients and antibodies against the human α6 integrin recognize a similar 70-kDa protein present in bovine gingival lysates or tumor cell lines (Bhol *et al.*, 1997).

Role in Embryonic Development and Cell Differentiation

The expression of specific adhesion molecules in the embryo is crucial for the migration of cells and the differentiation of tissue (Steinberg and Takeichi, 1994). The development of organs requires numerous cell-cell and cell-ECM recognition processes. In animal models, it has been demonstrated that adhesion molecules are involved in early developmental processes like the maturation of gametes, fertilization, implantation, and gastrulation (Howard and Smith, 1993; Ransom *et al.*, 1993; Sutherland *et al.*, 1993; Tarone *et al.*, 1993; Joos *et al.*, 1995).

The expression of adhesion molecules during development is both site- and time-specific. For instance, in chicken embryos, the expression of cadherin 6B in the migrating neural crest cell ceases after neural tube closure. The cells begin to express cadherin 7 and occupy dorsal and ventral roots (Nakagawa and Takeichi, 1995).

In the epidermis, proliferation is restricted to the basal layers of keratinocytes, and cells experience terminal differentiation as they migrate through the higher layers.

As in mature epidermis, the integrins are confined to the basal layers of keratinocytes during human epidermal development. The expression of integrin subunits during the development of human palm and sole skin has been studied by immunofluorescence microscopy (Hertle *et al.*, 1994). α3 and β1 subunits are constantly expressed by basal cells prior to stratification and during epidermal development. The α2 subunit was detected in small patches of basal cells prior to stratification, and thereafter was found in the entire basal layer, with greater fluorescence in developing sweat glands. The α5 subunit was observed after mid-development and then primarily on developing sweat glands. The α6 and β4 subunits were peribasally expressed before stratification, and thereafter became concentrated at the basal pole in contact with the basement membrane. Investigators have found that after keratinocyte differentiation begins, keratinocytes lose adhesiveness to fibronectin, laminin, and collagen, and β1 integrins are downregulated; this allows for the migration of keratinocytes out of the basal layer (Hertle *et al.*, 1994; Hodivala and Watt, 1994).

Final differentiation of tissue may involve the combination of different subtypes of adhesion receptors. In neurite outgrowth, the differentiation process involves adhesion mediated by α8β1 integrins, N-CAM, and N-cadherin (Harper *et al.*, 1994; Muller *et al.*, 1995).

The expression of adhesion receptors is associated with the segmental organization of organs. In chicken and mouse brains, there is a specific expression of different types of cadherins depending on the age of the embryo. E-cadherin, R-cadherin, cadherin-6, and cadherin-11 are expressed in a restricted fashion in the early neuromeric period (Ganzler and Redies, 1995; Matsunami and Takeichi, 1995; Inoue *et al.*, 1997; Korematsu and Redies, 1997). Each one of these cadherins shows an unique expression that is associated with the segmental organization of the early embryonic brain. Therefore, it is possible that different cell groups, linked by adhesion molecules, work as units during morphogenesis, and that the expression of certain adhesion molecules defines the limits of anatomic or functional areas in the brain.

Studies in the expression of adhesion receptors during tooth development have also been performed in mice (Obara and Takeda, 1993, 1997). Different patterns of N-CAM expression during the stages of tooth development and different expression patterns of N-CAM between molar and incisor development suggest that N-CAM plays an essential role in the formation of the basic structure of teeth and periodontal tissue (Obara and Takeda, 1993, 1997).

Recently, experiments using knockout mice have provided important information on the roles of adhesion molecules *in vivo*. α3 integrin null mice showed disorga-

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nization of the epidermal basal membrane and formation of blisters caused by the rupture of the basement membrane (DiPersio *et al.*, 1997). α6 integrin null mice develop detachment of the epidermis from the dermis and absence of HDS (Georges-Labouesse *et al.*, 1996b). Moreover, mice with mutations of the adhesion receptor ligands can develop structural abnormalities. Fibronectin null mice have mesodermal defects, absence of somites, and vascular defects (George *et al.*, 1993; Georges-Labouesse *et al.*, 1996a).

Several factors should be considered in interpretation of the results from knockout mice studies. In the expression of maternal m-RNA, two or more molecules may share the same function, and the presence of two genes expressing the same protein has to be excluded before any conclusions can be reached (Hynes, 1996). While these studies provide major advances, several gaps in knowledge remain, and these will likely be addressed by future research. Nonetheless, it is evident that adhesion receptors play a vital, critical, timely, and specific role in organ and tissue development during embryogenesis.

Role in Leukocyte Functions and Inflammation

Leukocyte homing (LH) and recirculation are processes that protect the body against microbial invasion. Homing refers to the selective migration of leukocytes to inflamed tissues. The LH process is facilitated by the expression of specific adhesion molecules on the surfaces of tissues and lymphocytes (Rott *et al.*, 1996). Before the immune system cells reach the injured tissue, several steps are necessary. These mechanisms involve deceleration, attachment, and diapedesis of leukocytes through the endothelium (Bargatze *et al.*, 1995; Berlin *et al.*, 1995; Salmi *et al.*, 1997). These phenomena are comprised of sequential interactions between leukocyte surface receptors and ligands on the vascular endothelium.

Leukocyte extravasation has been divided into four steps: primary adhesion, rapid lymphocyte "activation", activation-dependent "arrest", and diapedesis (Butcher and Picker, 1996). Primary adhesion involves the interaction of the leukocyte sLe^x, CLA, fucosylated structures, and L-selectin with MAdCAM-1, E-selectin, P-selectin, and CD34 adhesion molecules on the endothelium surface. Together, these molecules form a loose adhesion that permits leukocyte rolling and deceleration to occur along the vessel wall (Berg *et al.*, 1993; Smith, 1993; Taylor *et al.*, 1996).

Rapid lymphocyte "activation" is the result of the interaction between several leukocyte cytokines (*e.g.*, GM-CSF, IL-5), chemokines (IL-8, monocyte chemotactic peptide-1, macrophage inflammatory protein-1b) and chemoattractants (C5a) with leukocytes that express complementary receptors (Huber *et al.*, 1991; Yong and Linch, 1993; Lloyd *et al.*, 1996). The activation of leukocytes increases the affinity between integrin heterodimers bound to its surface and ligands present in the endothelium (Honda *et al.*, 1994; Perez-Villar *et al.*, 1996). However, recent studies have shown that the interaction of chemokines with their complementary receptors on the leukocyte surface is not enough to activate the integrin heterodimers and promote the binding of leukocytes to the endothelium (Butcher and Picker, 1996).

Following leukocyte activation, the interaction between leukocyte integrin heterodimers and endothelial immunoglobulin superfamily ligands results in a firm adhesion of leukocytes to endothelium (Butcher and Picker, 1996). In this step, the integrin heterodimers α4β1, α4β7, β7, and β2 on the leukocyte interact with the ICAM-1, ICAM-2, VCAM-1, and MAdCAM ligands present on the endothelium (Carlos and Harlan, 1994; Butcher and Picker, 1996). Patients with the leukocyte adhesion deficiency type I have a deficient or absent expression of the β2 leukocyte integrin. The neutrophils and monocytes of these patients fail to migrate to inflammatory sites (Kishimoto *et al.*, 1989; Harlan, 1993; von Andrian *et al.*, 1993). Characteristically, the lymphocytes, eosinophils, and plasma cells of these patients are not affected. However, this characteristic is lost when the β1 integrin or its ligand VCAM-1 is blocked (Baron *et al.*, 1993; Weg *et al.*, 1993). These findings suggest that either different mechanisms involving adhesion molecules are present in different types of leukocytes or that different types of leukocytes have alternative mechanisms for the activation-dependent "arrest" step.

Leukocytes migrate across the endothelium through intercellular junctions in a process called diapedesis. In this process, there is an interaction between PECAM-1, β1, β2, and β7 integrins expressed on the leukocyte with the PECAM-1, ICAM-1, and VCAM-1 endothelium ligands (Meerschaert and Furie, 1995; Berman *et al.*, 1996; Liao *et al.*, 1997; Romanic *et al.*, 1997). In summary, it is believed that selectins are mainly involved in leukocyte rolling, the integrins and their ligands in the "arrest" step, and the PECAM-1 in leukocyte migration.

The expression of several adhesion molecules such as ICAM-1, VCAM-1, α2β2, E-selectin, and L-selectin in oral tissue has been reported (Crawford and Hopp, 1990; Moughal *et al.*, 1992; Crawford and Watanabe, 1994; Gemmell *et al.*, 1994). It is possible that the same mechanisms described above for leukocyte homing and migration occur during the inflammatory process of the gingiva and oral mucosa.

In the skin, inflammation depends, in part, on the

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ability of the Langerhans cells (LC) to migrate from the epidermis to the lymphoid nodules and on the appropriate leukocyte homing to the skin. The homing of leukocytes to the skin is mediated by the interactions of CLA+ T-cells with endothelial E-selectin (Berg *et al.*, 1991; Rossiter *et al.*, 1994). It has been suggested that circulating memory cells can be rapidly mobilized to the skin if the expression of the CLA antigen is raised in response to antigen challenge. Recently, investigators have elucidated the structure of the CLA antigen (Fuhlbrigge *et al.*, 1997). CLA is an inducible carbohydrate modification of the P-selectin glycoprotein ligand (PSGL-1), a glycoprotein that is expressed on all human peripheral blood cells. The authors suggested that, following a specific stimulus, PSGL-1 is glycosylated by the fucosyltransferase VII and transformed into the CLA (Fuhlbrigge *et al.*, 1997). Expression of the CLA antigen on lymphocyte surfaces has been demonstrated *in vitro*, after exposure to cutaneous allergens and bacterial toxins (*Staphylococcus aureus* or *Streptococcus* bacteria) (Santamaria Babi *et al.*, 1995b; Leung *et al.*, 1995). These experiences may exemplify some of the stimuli that induce the glycosylation of PSGL-1. CLA antigen expressed on lymphocyte surfaces also interacts with the very late antigen 4 ($\alpha 4\beta 1$ integrin), VCAM-1, Lymphocyte function associate antigen-1 ($\alpha L\beta 2$ integrin), and ICAM, during the endothelial migration of leukocytes to the skin (Santamaria Babi *et al.*, 1995a). Recently, investigators have observed a selective accumulation of CLA+ cells in the epithelium of skin and oral mucosa affected with lichen planus (Walton *et al.*, 1997). This observation may suggest that CLA+ cells may play a role in the homing of leukocytes to the oral mucosa.

Adhesion molecules are also involved in leukocyte migration from the skin to lymph nodes. The expression and function of E-cadherin in LC have been recently studied. Murine LC bind to keratinocytes through the expression of E-cadherin (Tang *et al.*, 1993). In mice, E-cadherin expression is decreased on LC after exposure to contact allergens. Investigators also found that during T-cell activation, the LC that migrate from the skin to lymph nodes have low E-cadherin expression (Tang *et al.*, 1993). IL-1 and Tumor Necrosis Factor α (TNFα) have been shown to reproduce the effects of contact allergens on LC (Schwarzenberger and Udey, 1996). The authors suggest that contact allergens induce epidermal production of IL-1 and TNFα; these cytokines may influence E-cadherin expression by LC. Preliminary results show that human LC also express E-cadherin, but this observation has not been confirmed (Blauvelt *et al.*, 1995).

Role in Apoptosis

Genetically encoded cell death, or apoptosis, is a key mechanism for normal cell growth and death. Abnormalities in this balance contribute to pathologic states such as oncogenesis and autoimmunity. Most types of normal cells require attachment to an extracellular matrix to survive. The lack of adhesion to the ECM has been shown to trigger apoptosis (Frisch and Francis, 1994). The anchorage to ECM is mediated by adhesion receptors, mainly by the $\beta 1$ integrin subfamily receptors (Hynes, 1992; Scott *et al.*, 1992; Mohri, 1996). In epithelial cells, the blockage of the integrin receptors with RGD peptides detaches them from the substrate and triggers cellular changes similar to apoptosis (Frisch and Francis, 1994). The mechanism by which integrins regulate programmed cell death is not completely understood. In general, it is believed that the failure to bind to a specific ligand may trigger intracellular pathways that result in apoptosis.

In normal epidermis, $\alpha 1\beta 1$, $\alpha 2\beta 1$, and $\alpha 3\beta 1$ integrin receptors have been shown to bind to native type I collagen and to provide anchorage for epidermal cells (Staatz *et al.*, 1991; Gullberg *et al.*, 1992; Scott *et al.*, 1992). It has also been shown, *in vitro*, that binding of $\beta 1$ integrins to fibronectin substrate delays apoptosis (Scott *et al.*, 1997). Further, apoptosis is enhanced by the addition of $\beta 1$-blocking antibodies to cultured melanocytes attached to fibronectin (Scott *et al.*, 1997). Similarly, suppression of apoptosis was observed when melanocytes were cultured on immobilized anti- $\beta 1$ antibodies.

Alterations of the normal conformation of the ECM, such as that observed in malignant tumors, will trigger apoptosis of normal cells but support the survival of malignant cells. It has been observed that melanoma cells express $\alpha V\beta 3$ integrin, a molecule that acts as a receptor for fibrinogen and denaturated collagen. The expression of the $\alpha V\beta 3$ integrin by melanoma cells allows these cells to survive in degraded collagen (Montgomery *et al.*, 1994). But the expression of the $\alpha V\beta 3$ integrin by melanoma cells is not the only mechanism by which these cells prolong their life. Interestingly, when the human metastatic melanoma cell line SKMEL28 was cultured in suspension in the absence of exogenous growth factors, it was resistant to apoptosis (Scott *et al.*, 1997). The authors suggest that an aberrant mechanism that regulates integrin signaling may contribute to the fibrinogen-independent survival of this cell line (Scott *et al.*, 1997).

The intracellular pathways triggered after integrin activation may prevent apoptosis in some cells and may provoke apoptosis in others. For instance, in CD11b/CD18-deficient mice, the $\beta 2$ integrin is involved in chemoattractant-induced leukocyte adhesion. In these mice, extravasated leukocytes show a significant delay in apoptosis. It is suggested that CD11b/CD18 may trigger neutrophil apoptosis as a contra-regulatory mechanism to eliminate cells that have reached the end of their use-

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ful life span in inflamed tissues (Coxon *et al.*, 1996). Similarly, binding of eosinophils VLA-4 (β1 integrin) to fibronectin, *in vitro*, results in prolonged eosinophil survival (Higashimoto *et al.*, 1996). The investigators have suggested that regulation of eosinophil cell death may facilitate the accumulation of eosinophils at the allergic inflammatory sites.

There are some data on the intracellular pathways that are triggered by integrins in cell survival. Investigators have reported that transfection of β4 integrin to a carcinoma cell line induces the expression and probably the activation of the p21 protein, resulting in growth arrest and apoptotic death (Clarke *et al.*, 1995). The activation of integrin receptors may also trigger intracellular pathways that prevent apoptosis. It has been demonstrated that the binding of α5β1 integrin to fibronectin up-regulates the expression of the anti-apoptotic protein bcl-2, prolonging the survival of Chinese hamster ovary cells (Zhang *et al.*, 1995).

Current research suggests that cells can activate integrin and growth factor receptor molecules producing either growth or apoptosis (CS Chen *et al.*, 1997). The authors proposed that cells may be able to sense their degree of extension or compression and choose accordingly whether individual cells will grow or die, by activating the appropriate receptor (CS Chen *et al.*, 1997). The current state of knowledge indicates that the expression of cell adhesion receptors and the interaction receptor-ligand are important in the homeostatic control of cell survival. Manipulation of these interactions may be a future therapeutic alternative for diseases in which the regulation of programmed cell death is altered.

Role in Neoplasia

Tumor growth and metastasis involve abnormal cell cycle control, invasion of adjacent tissues, cell detachment from the primary site, and movement through lymphatic or blood vessels. As previously discussed, adhesion molecules participate in normal cell development, proliferation, and migration. The lack or aberrant expression of specific adhesion receptors may contribute to tumor growth and metastasis.

The presence of E-cadherin on the cell surface prevents cell expansion or tumor progression, most likely by keeping cells anchored to neighboring cells. Dysfunction of E-cadherin, or the E-cadherin-catenin cell adhesion complex, may allow for detachment of cancer cells from primary tumor nodules and contribute to cancer invasion and metastases (Frixen *et al.*, 1991; Shimoyama *et al.*, 1992; Peifer, 1993; Shiozaki *et al.*, 1996; H Chen *et al.*, 1997). Alterations in the expression of E-cadherin have been found in esophageal carcinoma, gastric carcinoma, breast cancer, bladder carcinoma, prostate, and head and neck carcinomas (Kuniyasu *et al.*, 1993; Troyanovsky *et al.*, 1993; Andrews *et al.*, 1997; Charpin *et al.*, 1997). It appears that abnormal E-cadherin expression is also associated with invasiveness and the metastatic ability of skin carcinoma. Normal skin expresses E-cadherin throughout intercellular spaces of epidermal cells, although lower amounts of E-cadherin are found on the basal cell layer. Strong expression of E-cadherin was found in tumor cells of basal cell carcinoma, whereas a marked decrease or loss of E-cadherin expression was evident in tumor cells of squamous cell carcinoma (Tada *et al.*, 1996). These findings correlate with the lower metastatic potential of basal cell carcinomas and with the higher metastatic rate of squamous cell carcinomas.

The expression of some adhesion molecules affects the characteristics of malignant cells. The expression of the αVβ3 integrin in melanoma cells is correlated with a high degree of malignancy and increased frequency of metastases (Felding-Haberman *et al.*, 1992). Experimental studies have demonstrated that the activation of this heterodimer and of α5β1 stimulates the production of the protease, metalloproteinase 2. This enzyme degrades fibrinonectin and facilitates melanoma invasion of basement membrane matrices (Seftor *et al.*, 1992, 1993).

Oral squamous cell carcinomas also express particular integrin heterodimers that facilitate invasion and metastasis (Zhang *et al.*, 1995). Researchers have demonstrated that the expression of the α6β1 integrin by malignant cells allows them to migrate readily onto laminin-1 substrate. Normal keratinocytes adhere poorly and are non-motile on laminin-1, probably due to the fact that normal keratinocytes are unable to assemble and express the α6β1 integrin complex (Zhang *et al.*, 1995). The elevated expression of the α6β1 integrin by malignant mucosal keratinocytes may promote their migration onto laminin, thereby promoting invasion and metastasis. It was also demonstrated that malignant oral epithelium neo-expresses αVβ6 integrin (Jones *et al.*, 1997). In this study, the authors suggest that the expression of the αVβ6 by oral squamous cell carcinomas may also be involved in tumor progression.

ICAM-3 expression in blood vessels also seems to play a role in angiogenesis and tumor growth. Investigators have found that endothelial cells from malignant nonlymphoid tumors, lymphomas, and benign tumors express ICAM-3. ICAM-3 expression is higher in immature areas of hemangiomas, but is absent on endothelial cells of healing wound vessels. Similarly, the αV integrin is expressed in angiogenic vessels of solid tumors and is barely detectable in mature blood vessels (Brooks, 1996). The identification of peptides that resemble angiogenic integrin ligands will allow for "targeted" chemotherapy. Recently, investigators coupled

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the anti-cancer drug doxorubicin with the αV integrin-binding-motif peptide (Arap *et al.*, 1998). The doxorubicin peptide conjugates were used to treat mice bearing human breast carcinoma xenografts. This strategy enhanced the efficacy of the drug and reduced its toxicity (Arap *et al.*, 1998). The design of similar chemotherapeutic strategies will significantly improve the prognosis for individuals suffering from many neoplastic diseases.

Concluding Remarks

The role of adhesion molecules is one of the most active frontiers of research in biology. Several studies have been reviewed indicating that biologic processes have multiple steps that are accompanied by the involvement of several adhesion molecules. The families of adhesion receptors are probably larger than is presently known. It is possible that future research will describe not only new families of adhesion receptors, but also subdivisions within families. There is every reason to speculate that molecules with the same or similar molecular structure may mediate different roles or functions based upon the environment into which they are placed. In addition, new functions and new interactions may be identified for the adhesion receptors that were discussed in this review. In the future, a clearer understanding of these molecules and their associated ligands will generate the synthesis of specific therapeutic agents that will have a guided or targeted purpose rather than a general or systemic effect. This new therapeutic intervention will be especially valuable in the treatment of cancer, in which current therapies are highly non-specific and cause high morbidity. Present information on cell adhesion molecules is only basic, fundamental, scanty, scattered, and not completely cohesive. It is quite possible that the information presented in this review may be completely transformed within a decade. However, the available information will continue to be the cornerstone for defining the normal physiology of many organ systems, which in turn will elucidate the pathogenesis of disease processes.

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