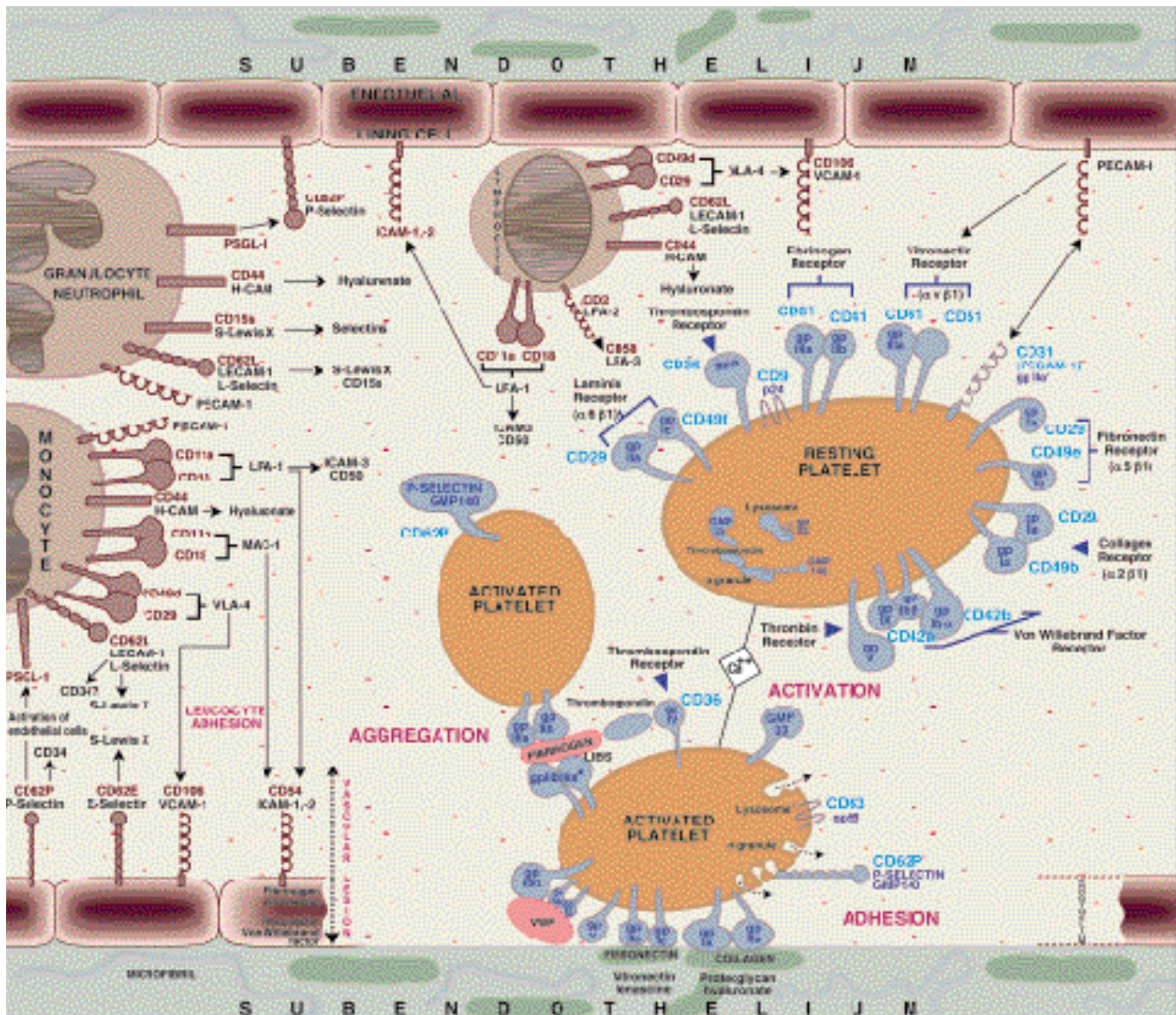


ADHESION MOLECULES

Introduction

Cell adhesion occurs when a plasma membrane adhesion receptor interacts with a molecule in the extracellular matrix or on the neighboring cell and when the liganded receptor forms a connection with the cell's own cytoskeleton. The reversibility of the process, which may oscillate through cycles of adhesion and detachment, enables cells to move with respect to one another or on the extracellular matrix. The process is controlled by the expression and function of adhesion receptors and by encounter with the corresponding ligands. Thus, cell adhesion is a major theme in normal biological processes and pathological disturbances involving cell-cell and cell-matrix interactions. Examples include: fertilization, embryogenesis, morphogenesis, tissue structure and repair, hemostasis, immune and inflammatory responses. Cell adhesion enables cells to be targeted to a particular location within tissues or in the body. In addition, many signaling molecules are docked in adhesion sites and their activation results in the production of messages which cross-talk with cell signaling pathways. Studies have shown that adhesion participates in the regulation of differentiation, proliferation and apoptosis. Thus cell adhesion has a dual morphogenetic and signaling function which explains its pleiotropic impact in normal biology and pathology.

Adhesion Receptor Classification





Adhesion receptors are type-I transmembrane proteins which may be classified in different subfamilies according to structural and functional homologies. ICAMs (1 to 4), VCAM-1, MadCAM and PECAM belong to the immunoglobulin gene superfamily. They are expressed generally in leukocytes and endothelium. These CAMs are generally counter-receptors for leukocyte integrins. Neural-CAMs, made of fibronectin III repeats and immunoglobulin-like moieties, play a main role in neural plasticity. They bind homotypically and in some instances to integrins. Cadherins, which show homophilic Ca^{++} dependent binding (1), and related homologues desmoglein and desmocollin (2), are main intercellular adhesion molecules. Selectins are lectins expressed on leukocytes (L-selectin) or platelets (P-selectin) and endothelium (P- and E-selectins). They recognize sialomucins or proteins such as PSLG-1 or ESL-1 which bear (sulfated-) sialyl Lewis x carbohydrate moieties. Among other functions, selectins support leukocyte rolling on the endothelium (3). Integrin / heterodimers are major receptors for extracellular matrix proteins, for example, laminins, collagens, RGD-containing ligands but also for cell-borne molecules (4). Sixteen α chains and eight β chains have been characterized. These associate to form 21 different integrin / heterodimers, each showing a defined ligand binding specificity. Ligand binding involves the formation of a quaternary complex between the ligand, a cation and sequences in the N-terminal regions of both α and β subunits. Each cell type express a repertoire made of different integrins which is regulated developmentally and after cell activation. Hyaluronate containing molecules are ligands for RHAMM or CD44 (5). The genetic heterogeneity of cell adhesion receptors is amplified by developmentally regulated mRNA alternative splicings that result in the expression of functionally different isoforms. These can be distinguished by the sequences of the ectodomain, for example, CD44, or of the cytoplasmic tails, for example, integrin α and β subunits.

Adhesion receptor	Structural feature	Counter-receptor	Cellular function	Biological and pathological implication
ICAM, vCAM, MadCAM	IgG repeats	integrins	leucocyte-leucocyte leucocyte-endothelium interactions	Leucocyte trafficking Inflammatory and Immune responses
NCAM, L1, Thy1	IgG and fibronectin repeats	homotypic binding	neural cell-cell adhesion	Neural development and plasticity
Cadherins Desmogleins Desmocollins	cadherin repeats	homotypic Ca^{++} - -dependent binding	<i>adherens</i> junctions and desmosome components	Tissue structure and repair. Invasion-metastasis
Selectins	sugar binding domain	sialomucins, PSLG-1, ESL-1	leucocyte-endothelium interactions	Leucocyte rolling
Integrins	α / β heterodimers	Mg^{++} -dependent binding of ligands on cell (CAM) and in ECM	promiscuous	promiscuous, all situations listed above
CD44	numerous splice variants	hyaluronans	cell-ECM interaction	Leucocyte activation and trafficking Invasion-metastasis

Adhesion Regulation and Signaling

The regulation of adhesion at the level of receptor-ligand interactions involves modulation of receptor number and type. This can occur by synthesis, by secretion from intracellular stores or by shedding through proteolytic events. Regulation of integrin function by affinity modulation through allosteric conformational changes is of major biological significance. Physiologically, these conformational changes are supposed to be elicited after cell activation by the interaction of specific cytosolic or cytoskeletal proteins with the cytoplasmic tails of the receptor (6). The β subunit plays an important role in this affinity regulation since epitopes for integrin activating antibodies lie on the β chain. Antibodies may affect integrin function by a direct stimulation of the conformational change or by allosteric effect, that is, by binding to epitopes in the α chain which are induced



or attenuated in the ligand-occupied integrin, thereby stabilizing the active or the inactive conformation (7). Obviously such antibodies are powerful tools to study integrin function in the frame of cellular activation.

Adhesion receptors are often found clustered in defined anatomical and functional structures. In connection to intermediate filaments, desmocollins and desmogleins are part of desmosomes (2) and the integrin $\alpha 6 \beta 4$ occurs in the hemidesmosomes (8). In connection to F-actin, integrins, cadherins and ICAM-3 are clustered within focal or point contacts (9), adherens junctions (1) and uropods (10), respectively. The connection to F-actin is initiated by linker-molecules such as talin or filamin which bind to the β subunit of integrins (9), or by catenins which interact with cadherins and by ezrin/radixin/moesin-like molecules for ICAM or CD44 (11). Additional actin-bundling molecules e.g. vinculin and α -actinin help to strengthen these linkages.

The connection to F-actin depends on synergy between the function of GTP-binding proteins belonging to the rho subfamily which drive actin polymerization (12) and signals generated by receptor engagement and oligomerization. The nature of these signals remains elusive. However, transient protein tyrosine phosphorylations resulting from the activation of cytosolic tyrosine kinases are believed to play an important role. For example, FAK and c-src (9) are involved in integrin-mediated adhesion, while the activation of a helper-tyrosine kinase receptor bound in a cis-manner to the ectodomain of the adhesion molecule (13) plays a part in NCAM-mediated adhesion. These phosphorylations seem important also for the recruitment to adhesion sites of many cytoplasmic enzymes associated in a supramolecular signaling complex (14). They participate in securing or disassembling receptor-cytoskeleton connections and also collaborate with growth factor signaling to regulate proliferation, apoptosis and cell differentiation.

The cis-interaction of adhesion receptors with a growing list of heterologous plasma membrane molecules participates in a major way in adhesion regulation and signaling. The GPI-anchored receptor for urokinase plasminogen activator (uPAR) and the metalloproteinase MMP-2 (15) associate with integrins. By inhibiting integrin function and enabling directional proteolysis, uPAR-integrin binding appears essential for cell migration and tumor invasion (16). The association with CD47, seems critical for the signaling and adhesive functions of $\alpha v \beta 3$ and $\alpha 2 \beta 3$ integrins as well as for their binding to thrombospondin (17). The interaction between integrins and members of the transmembrane 4 superfamily (CD9, CD63, CD81) participates in integrin signaling, possibly by activation of tyrosine kinases or phosphatidylinositol 4-kinase (18). The binding of caveolin to the chain of integrins $\alpha 1 \beta 1$, $\alpha 5 \beta 1$, $\alpha v \beta 3$ specifies their association with the adaptor molecule SHC and enables anchorage-dependent control of proliferation (19). Receptors endowed with protein tyrosine phosphatase activity which associate with NCAM and cadherins, may participate in a control of cadherin-catenin phosphorylation and in the stability of adherens junctions (20).

Perspectives

Each cell adhesion system involves specific molecular reactions, and is regulated by and interferes with cell signaling. Collectively, these processes are orchestrated to yield biological responses such as those encountered during inflammation or wound-healing, angiogenesis and tumor invasion. The latter situations are reminiscent of the epithelial-mesenchymal transitions observed in development (21). The coordination of adhesion receptor function in the course of these responses may result from modulation of activity by growth factors or oncogenes of molecules such as phospholipases and kinases or GTPases which are in a position to trigger patterned interactive signaling cascades. In addition, the finding that a structural component of adherens junctions, β -catenin, is also directly implicated in the regulation of transcription as a key transduction element of the Wnt signaling pathway (21), opens new conceptual ways in considering how cell adhesion and gene expression are coordinated. A careful evaluation of adhesion receptor function and signaling may lead to a more profound understanding of many normal and pathological situations.

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