Integrins

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Integrins belong to a group of cell adhesion molecules (CAMs) which is a large group of membrane-bound proteins. They are involved both in cell attachment to the extracellular matrix (ECM) and in signal transduction from the ECM to the cells. They also take part in numerous biological activities, namely extravasation, cell-to-cell adhesion, cell migration, and function as receptors for certain viruses, including adenovirus, echovirus, hantavirus, foot-and-mouth disease, polio virus and severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2). CAMs also include selectins, cadherins, immunoglobulin superfamily and other molecules, including CD44. Cell adhesion molecules are classified using the CD nomenclature (from 1 to 130). Integrins receive and transmit biochemical and mechanical signals through the cell membrane in both directions. Signals which develop inside the cell lead to conformational changes of the molecule and transmission of integrin into a state which enables ligand binding. The name “integrins” has been coined to denote the function they have maintaining a multicellular organism as a whole. They significantly affect the integrity of the cytoskeleton–ECM connections.

Keywords: integrins ; eye ; cornea

1. Integrin Structure

Integrins are heterodimeric glycoproteins which serve a function of transmembrane receptors. They are composed of two chains, α and β, which can be joined together making 24 combinations of various heterodimers. These chains are noncovalently associated. The spatial structure of integrins resembles the human body [1][2][3][4]. The “head” is based on two “legs” which are changed into the transmembrane domain. Interactions between the α and β subunits usually take place in the “head.” The α chain is composed of a seven-bladed β-propeller joined with a thigh, calf-1 and calf-2 domains. This structure supports the integrin head. The last three or four blades of the β-propeller include domains that bind Ca^{2+}. The β chain is composed of βI, hybrid and PSI (plexin/semaphorin/integrin) domains and four cysteine-rich epidermal growth factor-like (EGF) modules. The βI domain contains Mg^{2+}. Divalent ions are essential for normal function of integrins. Each ion has a different function. Mn^{2+} and Mg^{2+} activate adhesion processes. Ca^{2+} ions, depending on concentration, may have an inhibitory or stimulatory effect. High Ca^{2+} concentration inhibits adhesion, whereas low Ca^{2+} concentration with optimal Mg^{2+} concentration stimulates binding of a ligand with an integrin [5].

2. Integrin Activation

Knowing the mechanism of integrin activation enables searching for new therapies of many diseases, e.g., cardiovascular diseases (venous emboli, myocardial infarctions), inflammatory diseases, allergies and metastatic processes. The presence and activity of integrins depend on numerous factors, which can be activators or inhibitors. These include hormones, cytokines, mediators of systemic inflammation, active components of the complement system, active oxygen species, endotoxins or pharmacological compounds. A change in the expression of integrin receptors usually takes place at the transcription level. Integrin activation leads to molecular transformation, which enables ligand binding [2].

Intracellular domains of both chains bind directly or indirectly with the cellular actin-based cytoskeleton [1][6]. Depending on the signal direction, integrin activation may take place in two ways: as outside–in signaling or inside–out signaling. In the case of outside–in signal transduction, ligand binding to extracellular domains of an integrin causes a shift of the subunit “head” segments, elongation of the integrin in the “knee” region and extending the whole structure. As a result, the domains forming the “legs” move apart. The transmembrane and cytoplasmic regions of both subunits are moved apart, too. This way, the integrin molecule is activated, showing a higher affinity to ligands. Then, clustering occurs, which in turn initiates adhesion processes between the cell and the extracellular matrix. In the case of inside–out activation, ligand conjugation is not necessary to activate an integrin. Such activation is mediated by intracellular proteins bound to the cytoplasmic skeleton: kindlin, talin and migflin [2].

Integrins occur in three various spatial configurations: closed, activated (extended-closed) and active (extended-open) conformations. During transition from a closed to activated conformation, there occurs extension of the integrin between calf-1 and thigh in the α subunit and between I–EGF-1 and I–EGF-2 in the β subunit [7].

The integrin molecule is rich in cysteine residues which form disulfide bridges. A transition of an integrin from its inactive form to a form enabling ligand binding is preceded by reorganization of disulfide bonds inside the molecule. This reaction is catalyzed by protein disulfide isomerase (PDI). An example of PDI participation in integrin activation is the process of platelet aggregation. The PDI count is much lower in inactive platelets than during activation. Using anti-PDI antibodies, inhibition of blood platelet aggregation was observed. Other examples involve processes taking place in vascular endothelial cells. Mn^{2+} ions initiate formation of relatively stable complexes between the $\alpha_V\beta_3$ integrin and PDI [8].

3. Integrin Classification

Vertebrates have 18 α and eight β subunits, which form various heterodimers. Integrin heterodimers contain a number of combinations of α and β subunits. Depending on the type of the ligand bound, integrins can be classified as collagen-binding integrins ($\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_{10}\beta_1$, $\alpha_{11}\beta_1$), integrins recognizing the RGD motif (the triple amino acid sequence arginine–glycine–aspartic acid ($\alpha_5\beta_1$, $\alpha_V\beta_1$, $\alpha_V\beta_3$, $\alpha_V\beta_5$, $\alpha_V\beta_6$, $\alpha_V\beta_8$, $\alpha_{IIb}\beta_3$, $\alpha_8\beta_1$)), laminin-binding integrins ($\alpha_3\beta_1$, $\alpha_6\beta_1$, $\alpha_7\beta_1$, $\alpha_6\beta_4$) and leukocyte-binding integrins ($\alpha_L\beta_2$, $\alpha_M\beta_2$, $\alpha_X\beta_2$, $\alpha_D\beta_2$). The β_2 integrin subunit (CD18) is able to couple to one of the α subunits (α_L-CD11a, α_M-CD11b, α_X-CD11c, α_D-CD11d) to form lymphocyte function-associated antigen-1 (LFA-1/$\alpha_L\beta2$/CD11a/CD18), macrophage-1 antigen/complement receptor 3 (Mac1/CR3/$\alpha_M\beta2$/CD11b/CD18) and complement receptor 4 (p150,95/CR4/CD11c/CD18). The CD11a/CD18 is present mainly on all leukocytes, whereas CD11b/CD18, CD11c/CD18 and CD11d/CD18 are found on myeloid cells. The $\alpha_M\beta_2$ integrin (also known as CR3, CD11b/CD18 or Mac-1) is expressed on phagocytic cells and engaged in the adhesion of leukocytes to the endothelium and microbial opsonization. Ligands for CR3 contain the complement component iC3b, the intercellular adhesion molecule (ICAM-1) and coagulation factors such as fibrinogen and factor X [1][2][9][10][11].

Another classification is based on the presence of the αI domain. Belonging to one of the integrin families depends on the β chain (with the most important β_1, β_2 and β_7 chains) combined with various α chains. Each of the β subunits may form a heterodimeric receptor with various α subunits. An exception is the α_V subunit, which binds several different β subunits, e.g., $\alpha_V\beta_1$, $\alpha_V\beta_3$, $\alpha_V\beta_5$, $\alpha_V\beta_6$. Since they may appear at 2–7 weeks after lymphocyte stimulation, β_1 integrins are called very late antigens (VLA) or CD29. They participate in the binding of cells with the extracellular matrix. They bind laminin, fibronectin, vitronectin, collagen and other proteins of the extracellular matrix; therefore, they serve an important function in cell adhesion to the background. They occur on numerous cells of the immune system. They are absent on erythrocytes. Eosinophils show a presence of the $\alpha_4\beta_1$ and $\alpha_6\beta_1$ integrins, $\alpha_4\beta_1$ and $\alpha_5\beta_1$ basophils, $\alpha_3\beta_1$, $\alpha_4\beta_1$ and $\alpha_5\beta_1$ mastocytes. Neutrophils contain all the β1 integrins, except for the $\alpha_4\beta_1$ integrin. On the other hand, β_2 integrins are present on cell membranes of all leukocyte populations. This subunit can be linked with one of the three α subunits which form the CD11a, CD11b, CD11c titer. The group of β_2 integrins contains the LFA-1, Mac-1 and GP-150/95 glycoproteins. The CD11a/CD18 integrin is called LFA-1 (leukocyte function-associated antigen) since these antigens are found only on leukocytes. The Mac-1 integrins occur in their inactive form on neutrophils, monocytes and NK cells. Activation and binding with ICAM-1 is caused by inflammatory factors. As a result, neutrophils are bound to endothelial cells [12][13].

Integrin ligands also include receptors, which belong to a family of immunoglobulin-like CAMs such as ICAM-1, vascular cell adhesion molecule 1 (VCAM 1). They occur, e.g., on the surface of endothelial cells. These connections are characterized by high bond strength. ICAM-1 is a ligand for the CD11a/CD18 integrin. ICAM-1 synthesis is triggered by TNF-α, IL-1 and interferon gamma (IFNγ), endotoxin. ICAM-2 binds to the CD11b/CD18 integrin. The CD11a/CD18 and CD11b/CD18 integrins play the most important role in the inflammatory process [14]. Integrins are also able to bind very different proteins of the extracellular matrix, e.g., fibronectin, fibrinogen, vitronectin, laminin, collagen, plasminogen, osteopontin, von Willebrand factor or sialoprotein of the matrix skeleton [15][16]. The alternative name for β_3 integrins is cytoadhesins. They play a major role in the adhesion and aggregation of blood platelets and in the formation of complexes. Recognizing the RGD sequence, they bind fibrinogen, vitronectin, fibronectin and von Willebrand factor. They include platelet adhesion gpIIb/IIIa (CD61/CD41) and receptor for vitronectin (CD61/CD51) which occurs on the endothelium and the macrophage cell membrane [17].

Integrin ligands may also include proteolysis-triggered endostatin (coming from type XVIII collagen), endorepellin and tumstatin. Moreover, integrins may also bind viper venom toxins called disintegrins, certain viruses and bacteria [12][18]. Various pathogens, e.g., echoviruses, adenoviruses, and herpesviruses use integrins to penetrate cells. Integrins may be receptors for SARS-CoV-2 and can be implicated in transmission and pathology of SARS-CoV-2 [3].

4. Integrin Function

Integrins play an important role in physiological and pathological processes, as well as in wound-healing processes. The specificity of the inflammatory process depends on adequate expression of adhesion molecules enabling leukocyte migration.

During inflammation, integrins enable white blood cells to cross the vascular wall. On the leukocyte membrane, β_2 integrins bind ICAM-1 whereas $\alpha_4\beta_1$ and $\alpha_4\beta_7$ bind VCAM-1 on endothelial cells [19][20]. The integrin α4 subunit can dimerize with either the β_1 or β_7 subunit to form the $\alpha_4\beta_1$ or $\alpha_4\beta_7$ integrin. During inflammation, $\alpha_4\beta_1$ promotes transendothelial lymphocyte migration into the inflamed tissue, whereas $\alpha_4\beta_7$ helps in lymphocyte migration into the intestinal mucosal lymphoid tissues [21]. In addition, the $\alpha_4\beta_1$ integrin can interact with vascular endothelial growth factor/VEGF receptor 2 (VEGF/VEGFR2) and/or contributes to VEGF functions in chronic lymphocytic leukemia (CLL) [22].

The adhesion and binding of leukocytes to the surface of the vascular endothelium result from the connection of the β_2 integrin of the leukocyte membrane with endothelial cells. A similar mechanism of adhesion to the vascular endothelium applies to circulating neoplastic cells. These interactions are essential for crossing the vascular barrier and forming metastasis. It has been demonstrated that the occurrence of β_4 and α_6 integrins on the cells of squamous cell carcinoma is increased. The CD11b/CD18 integrin (β_2) mediates responses to Gram-negative bacteria while interleukin 1 takes part in the migration of inflammatory cells. In the case of infection with Gram-positive bacteria, cells migrate via a CD11b/CD18-independent pathway [23][24][25].

Mutations in integrin subunits may cause various genetic diseases in humans. Three autosomal recessive diseases have been described: Glanzmann's thrombasthenia (mutations of the α_{IIb} and β_3 integrins), leukocyte adhesion deficiency (LAD)—caused by point mutations or deletion of a gene in the β_2 integrin—characterized by hereditary deficiency syndrome [26] and vesicular epidermal necrolysis caused by mutation of the $\alpha_6\beta_4$ integrin [27][28].

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