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Neutrophil integrin affinity regulation in adhesion, migration, and bacterial clearance

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Abbreviations: CR3, complement receptor 3; CR4, complement receptor 4; ICAM-1, intercellular adhesion molecule 1; MAC-1, macrophage-1 antigen; LFA-1, lymphocyte function-associated antigen 1; PMA, phorbol myristate acetate; fMLF, N-formyl-Met-Leu-Phe; LTB4, leukotriene B4; IL-8, Interleukin-8; NETs, neutrophil extracellular traps; GPCR, G-protein coupled receptor; ITAM, immunoreceptor tyrosine-based activation motif; LAD, leukocyte adhesion deficiency; PSGL-1, P-selectin glycoprotein ligand-1; FcγR , Fcγ receptor

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During an infection, neutrophils are the first immune cells to arrive armed to clear the invading pathogen. In order to do so, neutrophils need to transmigrate from the peripheral blood through the endothelial layer toward the site of inflammation. This process is in most cases dependent on integrins, adhesion molecules present on all immune cells. These molecules are functionally regulated by "inside-out" signaling, where stimulus-induced signaling pathways act on the intracellular integrin tail to regulate the activity of the receptor on the outside. Both a change in conformation (affinity) and clustering (avidity/valency) of the receptors occurs and many factors have been linked to regulation of integrins on neutrophils. Control of integrin conformation and clustering is of pivotal importance for proper cell adhesion, migration, and bacterial clearance. Recently, gelsolin was found to be involved in β_1-integrin affinity regulation and cell adhesion. Here, I summarize the role of neutrophil integrin regulation in the essential steps to reach the site of inflammation and clearance of bacterial pathogens.

Integrin Affinity Regulation

The ability of leukocyte to adhere, migrate toward a site of inflammation, or phagocytose opsonized pathogens is largely dependent on cell surface adhesion molecules called integrins. Integrins are a family of 26 proteins that are composed of non-covalently linked α and β subunits. Until now, eight different β subunits and 18 different α subunits have been described on human cells that form 24 known α-β heterodimers.[1] Neutrophils mainly express β_2-integrins, including $\beta_2\alpha_M$ (also CD18/CD11b, complement receptor [CR]3, or macrophage-1 antigen [MAC-1]), $\beta_2\alpha_L$ (also CD18/CD11a or lymphocyte function-associated antigen 1 [LFA-1]), and $\beta_2\alpha_X$ (also CD18/CD11c, CR4, or gp150/95).

Integrins on non-activated circulating immune cells are in an inactive state, being unable to bind their ligand. Signals induced by extracellular stimuli, such as chemokines and cytokines, converge at the intracellular integrin tail and lead to activation of the integrin, a process also known as inside-out control. Activation of integrin's ligand binding capacity is determined by two processes, a change in conformation (affinity) and/or clustering of integrins on the cell membrane (avidity/valency),[2] as depicted in **Figure 1**. Subsequently, extracellular ligand binding to integrins induces outside-in signaling, which regulate cell spreading, gene expression, cell proliferation, differentiation, and apoptosis.[3] Although the list of signaling and adaptor proteins involved in these processes are increasing, the precise mechanism by which all these proteins interplay at the intracellular integrin tail is still not completely understood.[4]

Integrin regulation is a very complex and dynamic process and over 150 proteins have been identified to be adhesion-associated.[5] The linkage of integrins to the cytoskeleton through talin-1 and kindlin-3 are essential in the regulation of integrin affinity.[6,7] Talin-1 binds with its head domain to the intracellular tail of β_1, β_2, and β_3 integrin. The talin-1 tail

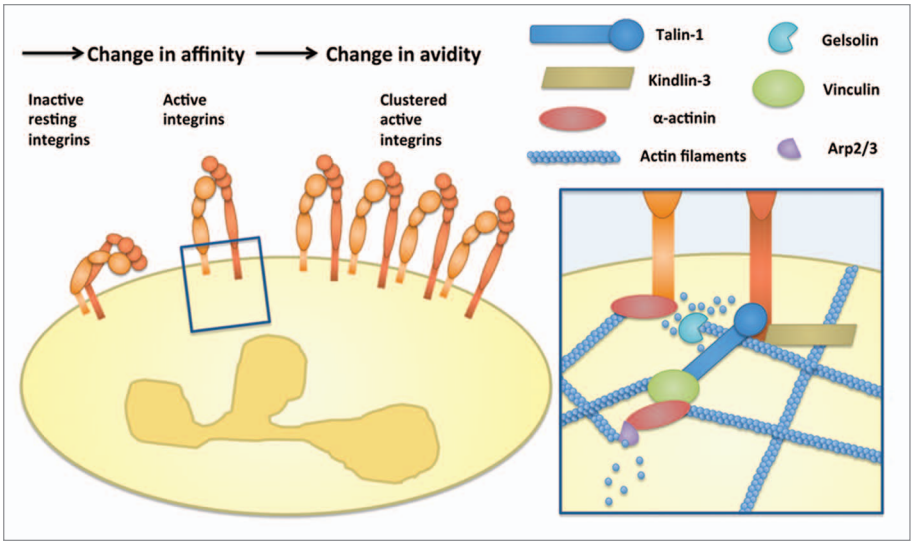

Figure 1. Schematic representation of neutrophil affinity and avidity regulation. On resting immune cells, integrins are in an inactive state with their ligand binding domains facing the cell membrane. Upon activation, α- and β-integrin transmembrane domains separate and the extracellular ligand binding domains are unfolded and accessible for ligand binding (change in affinity). Additionally, integrins can cluster together on the cell membrane (change in avidity). The proteins involved in the molecular mechanisms responsible for integrin affinity and avidity regulation include, among many others, talin-1, kindlin-3, α-actinin, vinculin, arp2/3, gelsolin, and actin.

domain can also weakly bind to the integrin's intracellular tail,[8] but is also known to bind vinculin and actin.[9] In turn, vinculin binds α-actinin and actin,[10] and can recruit arp2/3,[11] which induces actin polymerization. More recently, kindlin-3 was shown to be essential in the regulation of β_1-, β_2-, and β_3-integrins on blood platelets and leukocytes.[6,12] Kindlin-3 also binds to the β-integrin tail, but to a more distal site than talin-1, which enables simultaneous binding of both proteins.[6] For neutrophils, deletion of either talin-1 or kindlin-3 results in severe defects in firm endothelial adhesion,[12,13] emphasizing the major role these proteins have in the regulation of integrin affinity.

Although talin-1 and kindlin-3 are the two most studied integrin regulators, many other proteins have shown to modulate the integrin affinity or avidity, including many cytoskeletal proteins such as vinculin, paxillin, and α-actinin that directly link the integrin intracellular tail to the actin cytoskeleton.[14-16] Recently, it was shown that the protein level of gelsolin, an actin severing and capping protein, affects β_1-integrin affinity and cell adhesion in the lymphocytic leukemia cell line L1210 and histiocytic lymphoma cell line U937.[17,18] As detected by 2D-gel electrophoresis, adherent growing L1210 cells (L1210-A) with active β_1-integrins contained an almost 4-fold increase in gelsolin protein level compared with suspension growing L1210 cells (L1210-S) with inactive β_1-integrins.[18] Further evidence that gelsolin protein levels were related to β_1-integrin affinity regulation was obtained by modulating the protein levels in L1210 cells. Knockdown of gelsolin in L1210-A cells or ectopic overexpression of gelsolin in L1210-S cells decreased or increased high affinity β_1-integrins, respectively.[17]

The severing and capping activity of gelsolin is controlled by binding of Ca^{2+} and PI(4,5)P2.[19] Since gelsolin protein levels by itself affect β_1-integrin affinity, without the need to stimulate the cells, it was hypothesized that gelsolin has basal activity, which accounts for the necessary actin severing and capping activity in resting cells. This was supported by the use of jasplakinolide in L1210-A cells with high gelsolin protein expression and active β_1-integrins. Jasplakinolide increased actin polymerization, thereby counteracting the effects of gelsolin, which decreased the presence of active β_1-integrins on L1210-A cells. It is therefore tempting to speculate that the actin severing and capping activity of gelsolin in L1210 cells decreases the cytoskeletal constraints, and thereby, enables activation of β_1-integrins.

The concept that cytoskeletal constraints affect integrin affinity has been described before. For example, treatment of platelets with jasplakinolide decreased fibrinogen binding to integrin $\beta_3\alpha_{IIb}$.[20] Also, for neutrophils, jasplakinolide prevented the ability of neutrophils to firmly adhere to immobilized platelets upon stimulation with fMLF in in vitro flow experiments.[21] Not only integrin affinity is affected by cytoskeletal constraints, but also integrin avidity. Treatment of lymphocytes with cytochalasin D, which decreased actin polymerization, increased clustering of integrin $\beta_2\alpha_L$ or $\beta_1\alpha_4$.[22,23] Whether gesolin affects integrin avidity has not been investigated.

Integrin Regulation and Neutrophil Adhesion, Migration, and Phagocytosis

Proper integrin activation is essential for neutrophils to transmigrate from the vasculature into the tissue where these cells battle with invading pathogens (**Fig. 2**). Neutrophil migration is mediated by chemokines such as leukotriene B4 (LTB4), interleukin (IL)-8, or H_2O_2 produced by the inflamed tissue or by inflammatory cells present at the site of inflammation.[24,25] Most neutrophils transmigrate in the post-capillary venules were blood shear force is rather low. First, neutrophils start rolling via P-selectin glycoprotein ligand-1 (PSGL-1) binding to P-selectin or E-selectin on the vascular endothelium, which slows their speed significantly. Subsequently, extracellular stimuli, mostly activating G-protein coupled receptor (GPCR) on the neutrophil, initiate β_2-integrin inside-out signaling, shifting integrins into an active state. These active β_2-integrins subsequently bind to their ligand, for CR3 ($\beta_2\alpha_M$) intercellular adhesion molecule 1 (ICAM-1), which enables neutrophils to stop rolling and adhere to the vessel wall. Finally, neutrophils crawl over the vessel endothelium in the search for a suitable location to transmigrate, either paracellularly or in rare cases transcellularly,

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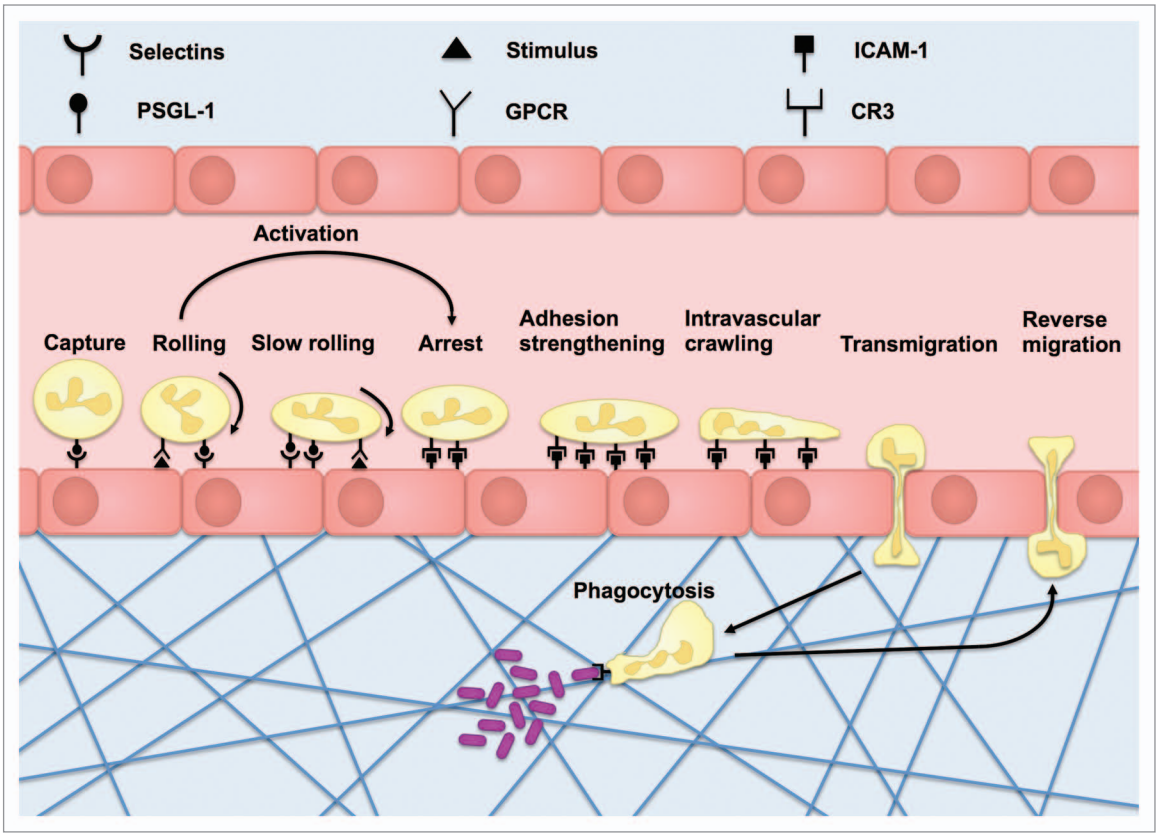

Figure 2. Schematic representation of the role of selectins and integrins in neutrophil rolling, adhesion, and migration from the vasculature into the tissues and back. Neutrophils start rolling via P-selectin glycoprotein ligand-1 (PSGL-1) that bind selectins on the vascular endothelium. Subsequently, extracellular stimuli activate G-protein coupled receptor (GPCR) on the neutrophil, which activates integrins, enabling them to bind intercellular adhesion molecule 1 (ICAM-1). Adhered neutrophils crawl over the vessel endothelium in the search for a suitable site to transmigrate into the underlying tissues. Subsequently, neutrophils battle invading pathogens, after which they can migrate back toward the vasculature.

into the underlying tissues.[26] Once in the tissues, neutrophil can migrate in an integrin-independent manner, by squeezing themselves through the matrix.[27] Here, neutrophils employ their anti-microbial activity by mechanisms that include (1) a powerful oxidative burst, (2) the release of proteolytic enzymes stored in granules, (3) phagocytic capacity, and (4) the formation of neutrophil extracellular traps (NETs).[28]

CR3 ($\beta_2\alpha_M$) is not only a cell adhesion receptor, it also functions as an opsonophagocytosis receptor trough the recognition of iC3b-opsonized bacteria. iC3b is a peptide from C3b generated in the complement activation cascade when factor I, in the presence of co-factor H, cleaves the α-chain of the C3b molecule. Phagocytosis of iC3b-coated bacteria is further enhanced when coated with IgG, which is recognized by Fcγ-receptors such as FcγRIII (CD16), FcγRIIA (CD32), or FcγRI (CD64) present on the surface of human neutrophils. Binding and cross-linking of FcγR by IgG opsonized particles triggers phosphorylation of tyrosine residues in so-called immunoreceptor tyrosine-based activation motif (ITAM) present in the associated γ-chain (FcγRI and FcγRIII) or FcγRIIA itself. This phosphorylation is dependent on protein tyrosine kinases such as Src and Syk initiating downstream signaling needed for efficient phagocytosis.[29] FcγR-mediated phagocytosis seems to be largely independent of CR3, since patients with leukocyte adhesion deficiency (LAD) as discussed in further detail below, show unaltered phagocytosis of Ig-coated red blood cells.[30]

FcγR and CR3 facilitate phagocytosis of opsonized particles by themselves, but involvement of both increases their efficiency significantly. It was shown that blocking CR3 with antibodies reduced FcγR-mediated phagocytosis without impairing FcγR-mediated binding of IgG for monocytes.[31] Also, binding of IgG to FcγR increased CR3 function on the mouse macrophage cell line RAW264.7 by inducing the lateral movement of CR3 to FcγR-containing phagocytic cups, enhancing iC3b binding.[32] Although it is clear that cross talk occurs between both receptors, the underlying mechanisms remain largely unclear.

It was thought that, once in the tissues, battling invading pathogens, neutrophils had a single final fate: death, after which they were cleared by macrophages. However, in the last decade, it has been appreciated that neutrophils can also reverse migrate from the tissue back into the bloodstream.[33,34] In vitro reverse migrated neutrophils presented a unique phenotype with high ICAM-1 and low CXCR1, a subset of neutrophils that is increased in the peripheral blood

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of patients with rheumatoid arthritis and atherosclerosis.[34]

Most of the observations on reverse migration have been obtained from in vitro experiments, or with in vivo zebrafish models. Since this process is not easily visualized in mammals, definitive proof of its importance is scarce. Recently, confocal intravital microscopy showed that approximately 10% of the transendothelial migration events were reverse migrating neutrophils in mice.[26] However, this is substantially different from in vivo zebrafish experiments, where almost all wound responsive neutrophils reverse migrate.[33] This discrepancy might depend on the differences in age, differences in tissue, or type of inflammation in these two in vivo systems.

The precise function of reverse migrating neutrophils in the inflammatory response has yet to be determined. It appears that reverse migrating neutrophils have an important role in the resolution of inflammation, a process that turns down the pro-inflammatory response and prevents unnecessary tissue damage. Recently, it was found that neutrophils can inhibit lymphocyte proliferation via direct interaction dependent on CR3 and PD-L1, thereby modulating the adaptive immune response.[35,36] Another possible function for reverse migrating neutrophils is antigen presentation, since neutrophils in mice that had been immunized against ova peptide transported FITC-labeled ova peptide from the site of injection to local lymph nodes.[37] Although the roles for reverse migrating neutrophils are far from elucidated, is becomes clear that neutrophils are not the standard short-lived cells with only an anti-microbial function.

Integrin Function in Health and Disease

The process of integrin-dependent adhesion and transmigration of neutrophils is crucial in the inflammatory response because impaired integrin function leads to recurrent bacterial infections, as observed in patients with a rare autosomal recessive disorder LAD. Three different forms of LAD have been described to date. In LAD-I, β_2-integrins are not present or expressed in low quantities on the cell surface.[38] Patients with LAD-II have a defect in post-translational fucosylation leading to impaired leukocyte rolling,[39] and patients with LAD-III show impaired affinity regulation of β_1-, β_2-, and β_3-integrins due to the functional loss of the essential integrin adaptor molecule kindlin-3.[40,41]

LAD-I is the most common and most studied leukocyte adhesion deficiency, affecting β_2-integrin function on leukocytes, particularly neutrophils. The molecular basis underlying LAD-I are mutations in exons 5 to 9 in the *ITGB2* gene coding for the β_2-integrin protein.[42] These mutations either lead to a total absence of β_2-integrins, or to a truncated form of the protein that usually results in low surface expression. LAD-I patients suffer from recurrent, life-threatening bacterial infections due to limited or no recruitment of neutrophils to the site of inflammation.

Most studies on LAD-I are focused on neutophils integrin regulation, adhesion, and migration, as these processes are essential for neutrophil to reach the site of inflammation. Neutrophils isolated from LAD-I patients are able to roll normally via selectins, but are unable to arrest in a β_2-integrin-dependent manner. It should be noted that neutrophil transmigration into the lungs during pneumonia seems to be unaffected in LAD-I patients,[43] which is in line with data that this type of migration is β_2-integrin independent, at least in rabbits[44] and mice.[45] These data show that, at least for β_2-integrins, there is tissue-specific dependency on β_2-integrin function for neutrophil transmigration.

Not only the presence of β_2-integrins is indispensable for proper neutrophil adhesion and migration, but also regulation of β_2-integrin affinity is essential. Patients with LAD-III have defects in kindlin-3, a protein important in β_1-, β_2-, and β_3-integrin affinity regulation.[6,12] Patients with LAD-III suffer from a rather mild LAD-I-like immunodeficiency with recurrent bacterial and fungal infections without pus formation despite a marked leukocytosis. Unlike for patients with LAD-I, patients with LAD-III express normal levels of β_2-integrins, but are not able to switch from inactive to active ligand-binding β_2-integrins, as was also observed in kindlin-3$^{-/-}$ mice.[6,12,40,41] In addition, LAD-III patients suffer from a severe bleeding tendency due to defective $\beta_2\alpha_{IIb}$-integrins, essential for proper platelet function.

Whereas substantial data are present regarding integrin deficiencies and the effects on neutrophil adhesion and migration, much less is known for their effects on direct binding and phagocytosis of opsonized invading pathogens. Neutrophils from LAD-I patients were defective in phagocytosing C3-opsonized bacteria, whereas uptake of IgG opsonized pathogens was largely unaffected.[46] Stimulation of neutrophils enhances their phagocytic capacity, which was largely dependent on switching β_2-integrins into an active confirmation, a mechanism known to be defective for neutrophils from patients with LAD-1.[47] It is expected that neutrophils from LAD-III patients are impaired for iC3b-mediated phagocytosis. However, it appears that the question whether phagocytosis by neutrophils from patients with LAD-III is affected has not been addressed to date.

Conclusions

It is clear that integrins, and especially β_2-integrins, are essential for proper adhesion, migration, and phagocytosis by neutrophils. Studies with neutrophils from patients with LAD sheds light on the essential role of integrins and integrin affinity regulation in cell adhesion, migration, and phagocytosis. Together with animal models such as talin-1 and kindlin-3-knockout mice, enormous steps have been made in understanding the general mechanisms underlying these processes, although many questions still remain unanswered.

Recently, it was shown that gelsolin affect β_1-integrin function via mechanisms that appear to be related to its actin-severing activity. Whether gelsolin affects integrins on primary human leukocytes or whether gelsolin might affect the affinity of other integrins such as β_2-integrins on neutrophils has to be determined.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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