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Neutrophil Chemotaxis and Polarization: When Asymmetry Means Movement

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1. Introduction

Neutrophils (also known as polymorphonuclear leukocytes or PMN), the first line of defense against intruding microorganisms, are produced in the bone marrow from stem cells that in turn proliferate and differentiate into mature neutrophils. They play an important role in host defense and contribute to inflammation-related tissue injuries. During inflammation, neutrophils extravasate across the endothelium that lines the blood vessel wall through a multistep process [1, 2], which includes rolling on and subsequent firm adhesion to endothelial cells.

Neutrophil migration through the vascular endothelial layer into lymphoid or inflamed tissues involves a dynamic regulation of cell adhesion in which new adhesions are formed at the cell's leading edge, [3] while filipodia and lamellipodia are generated as exploratory and motile projections and, coordinately, adhesions are released from the trailing edge [4].

For these events, the supply of adhesion molecules to the site of pseudopodial protrusion must be necessarily replenished in order to enable the cell to move forward. There is evidence that the membrane trafficking pathways that recycle adhesion receptors contribute to cell migration [5], which is crucial for polarization and migration in various cell types [6]. Preferential targeting of proteins to the leading or lagging edge of migrating cells is important for polarity and chemotaxis. Asymmetric distribution of proteins has implications beyond polarity and chemotaxis because these same proteins display characteristic localization patterns when cells undergo morphological changes in general. Several proteins have been identified as contributing to cell polarity organization and subsequent inflammatory-cell migration by regulating membrane trafficking. Ly49Q directs the organization of neutrophil polarization as well as neutrophil migration to inflammation sites by regulating membrane raft functions, reorganizing neutrophils in the presence of inflammatory signals, and maintaining neutrophil homeostasis in the absence of such signals [7]. In addition, regulated exocytosis plays a crucial role in conversion of inactive, circulating neutrophils into fully activated cells capable of chemotaxis, phagocytosis, and bacterial killing [8].

Polarity gives cells morphologically and functionally distinct spatial restriction to leading and/or lagging edges by relocating certain proteins or their activities selectively to the

poles. Polarization provides cells with morphological, functional, and sensitivity differences to the chemoattractant, altering the way the cell responds to a gradient. Thus, polarization generates a bipolar mechanosensory state with a dynamic leading edge for acquiring new contacts and signals, a stiff mid-body, and a sticky uropod that is dragged along the substrate and stabilizes the cell position in complex environments [9, 10]. Hence, integration of signals generated in both cellular poles leads to a coordinated movement of the leukocyte.

Chemotaxis is conceptually divided into motility, directional sensing, and polarity; however, chemotaxis typically incorporates these features. Many molecules involved in chemotaxis include both lipids and proteins and are localized on the membrane or in the cortex, specifically at either the leading or the lagging edge of polarized cells.

Freely diffusing chemoattractant or soluble molecular cues, known as Damage-associated molecular patterns (DAMP), are liberated from damaged tissue in high abundance. DAMP include Adenosine triphosphate (ATP), bacterial peptides, heat-shock proteins, chromatin, and galectins [11], providing short-lived or pulsatile directional information, in addition to longer-lived cues provided by constitutive or induced tissue-bound chemoattractants [11]. Beyond adhesive migration arrest, local reduction of promigratory signals is achieved by down-modulation of chemoattractant receptors, receptor desensitization, and ligand competition, whereas termination of chemoattractant activity occurs through uptake by neutralizing chemoattractant receptors and/or proteolytic degradation. After ligation, chemoattractant receptors become internalized and are either recycled to the leading edge or stored in vesicles in the uropod, thus limiting the availability of both the chemoattractant and its receptor [12]. The end result is a cascade of activation and adhesion events designed to uptake leukocytes along vessel walls, activate these for them to make stable adhesions, allow them to locomote along the endothelial surface, and to transmigrate across endothelial junctions and through the subendothelial basal lamina, guiding them onto the damage site (Figure 1) [13].

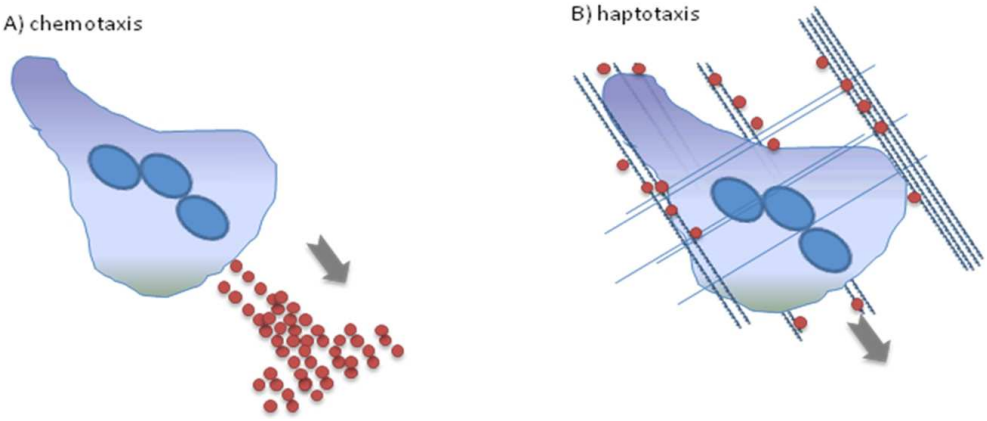

Fig. 1. Type chemotaxis in neutrophils. A) Chemotaxis triggered by soluble diffusing compounds leading to formation of the leading edge. B) Directed-mediated migration toward chemoattractants trapped on tissue structures.

2. Trafficking requirements

Trafficking leukocytes often reduce their migration speed, pause, and polarize toward the bound cell or the tissue structure to execute crucial functions including phagocytosis, cell-to-cell signaling, activation, and the release of cytokines or toxic factors toward an encountered cell.

At least three basic kinetic states govern leukocyte positioning in tissues, including fast migration (5 to 25 μm/min), slow and often locally confined movement (2 to 5 μm), and adhesive arrest, and these rapidly interconvert. Based on these kinetic states, leukocyte accumulation in tissues occurs by means of at least three distinct mechanisms: 1) local engagement of adhesion receptors causes individual leukocytes to stick and become immobilized at a specific spot; 2) degradation of promigratory signals causes cell populations to slow down or stop movement, and 3) loss of exit signals confines cells to a local microenvironment despite ongoing migration [14].

Complete migration arrest is mediated by activation of adhesion receptors on the moving cell followed by attachment to counter-receptors on other cells or on Endothelial cell migration (ECM) structures, leading to an immobilized cell. Within seconds, adhesion overrides ongoing promigratory signals; this is followed by cytoskeletal polarization toward the bound cell or the ECM structure [15].

3. Ensuring tightened adhesion

Endothelial cells (EC) are the critical substrate for leukocyte attachment and motility within the vascular lumen via adhesion molecules such as integrin, ligands whose expression is enhanced on activated ECs, which in turn react to molecules generated during infection and inflammation such as Tumor necrosis factor alpha (TNF- α), interleukin 1β (IL-1 β), and interleukin 17 (IL-17). Expression of these molecules can be further regulated through the cross-talk between EC and leucocytes; binding of PSGL-1 to P-selectin and E-selectin establishes the initial contact between neutrophils and activated ECs. Interaction of EC adhesion molecules (ICAM-1 and VCAM-1) with leukocyte ligands triggers the formation of docking structures or transmigrating cups [16, 17], which embrace adherent leucocytes [18]. Additionally, formation of pro-adhesive sites termed "endothelial adhesive platforms" (EAP) is determined by the existence of pre-formed, tetraspanin-enriched microdomains such as CD9, CD151, and CD81 [19].

Adherent leukocytes may transmigrate at the point of initial arrest, but sometimes rather locomote laterally to preferred sites of Transendothelial cell migration (TECM) [20, 21]; *in vitro* and *in vivo* luminal crawling is dependent on β2 integrins and its blockade appears to increase the incidence of trans- as opposed to paracellular cell migration [21]. The junctional adhesion molecule A (JAM-A), an adhesion molecule expressed on both EC and leukocytes [22], regulate integrin internalization and re-cycling [23].

There are other molecules and mechanisms that have been recently implicated in leukocyte motility; for example, it has been demonstrated both *in vivo* and *in vitro* that platelets enhance neutrophil TECM in inflammation, which is consistent with a mechanistic role for PSGL-1 for this response [24].

4. Neutrophil mobilization

Leukocyte interactions with the endothelial surface trigger cellular and sub-cellular events that initiate and/or facilitate leukocyte passage through the endothelium by interaction of docking structures with cytoskeleton via adaptor proteins such as vinculin, paxilin, and Ezrin, radixin, and moesin (ERM) proteins [18, 25], although Guanosine triphosphate (GTP)ases (RhoG and RhoA) induce actin polymerization leading to the formation of small membrane protrusions called apical cups or docking structures.

Once firm adhesion is established, two routes can be taken for transendothelial migration: the transcellular road, whereby neutrophils penetrate the individual EC, or the paracellular road, by which neutrophils squeeze between EC Figure 2.

A number of molecules at EC junctions actively facilitate leukocyte transmigration via a paracellular route such as Platelet endothelial adhesion molecular-1 (PECAM-1), Intracellular adhesion molecule-2 (ICAM-2), CD99, Endothelial cell-selective adhesion molecules (ESAM), and junctional adhesion molecules (JAM) [22, 26] and, according to *in vivo* and *in vitro* evidence, a sequence of events has been suggested that regulate neutrophil transmigration to EC walls and that include the following: (i) ICAM-1 and ICAM-2 on the luminal surface of EC and within the junction may provide a haptotactic gradient to guide neutrophils to EC junctions via their β2 partners (LFA-1 and MAC-1) [27]; (ii) once within junctions, endothelial-cell JAM-A (through interaction, possibly with LFA-1) [28], facilitates completion of neutrophil passage through the EC layer, and (iii) within the EC junction, homophilic interactions between endothelial and leukocyte PECAM-1 stimulates neutrophils to express the key leukocyte laminin receptor, integrin α6β1, on their surface, which facilitates neutrophil passage through the vascular basement membrane [29-31]. It is also noteworthy that signals from ICAM-1 activate Src and Pyk-2 tyrosine kinases, which phosphorylate VE-Cadherin, destabilizing its bonds and loosening endothelial cell-cell junctions [32].

The transcellular route is taken by some 20% of neutrophils and has been observed in a broad range of tissues including bone marrow, thymus, lymph nodes, pancreas, and the blood brain barrier [33]. Apparently, there is clear evidence for the formation of a transcellular pore requiring membrane fusion and displacement of cytoplasmic organelles during transcellular migration. Vesicular vacuolar organelles (VVO) are enriched at pore-formation sites, apparently providing additional membrane to the area and facilitating the fusion of apical and basal membranes in a process dependent on SNARE-containing membrane fusion complexes [34], and there is increasing evidence for a role for caveolin-1 in determining transendothelial migration route [35].

Carman et al. (2008) [34] have identified *in vitro* and *in vivo* the existence of protrusive podosomes on the basal side of crawling lymphocytes ; these protrusive podosomes appear to identify the cell's thinner peripheral areas rather than the perinuclear region in order to identify a pore formation-permissive site. These dynamic investigatory podosomes can then extend to form invasive podosomes, resembling invadopodia of metastatic tumor cells, which extend down into the EC, bringing the apical and basal membranes into close apposition.

5. Mobilization beyond the endothelium

Beyond the endothelium, migrating cells face two further barriers; the pericyte sheath, and the tough venular Basement membrane (BM) [36, 37]. Neutrophils have the ability to migrate through the pericyte sheath via both para- [38] and transcellular pathways

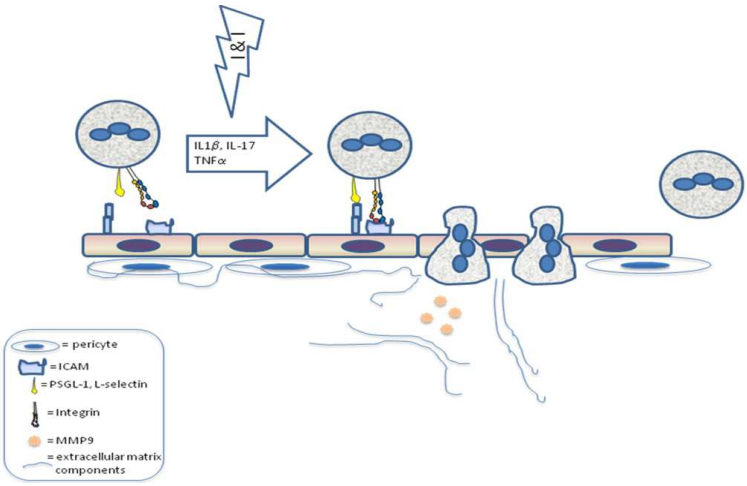

Fig. 2. Hypothetical sequence of events during neutrophil transmigration. Neutrophils are tethered by P- and E-selectin on endothelial cells and PSGL, L-selectin, and CD44 on neutrophils simultaneously participate in neutrophil rolling and activation. Endothelium activation by stimuli such as IL-1β, IL17, TNF-α promote transmigration dependent of molecules such as PECAM-1, ICAM-1, and JAM-A, thus unzipping the tight junctions and restoring themselves while TNF- α promote transmigration via ESAM. Neutrophils take trans- or paracellular routes. Postendothelial cleavage of structural proteins occurs by means of secreted or membrane-anchored matrix metalloproteases (MMPs). Abbreviations: Basement membrane (BM), Endothelial cells (EC), Platelet endothelial cell adhesion molecule (PECAM-1), Intracellular adhesion molecule-1 (ICAM-1), Endothelial cell-selective adhesion molecule (ESAM), Tumor necrosis factor- α (TNF-α) [39].

On the other hand, leukocyte penetration of the vascular BM depends on the vascular bed. Additionally, it has recently been shown that the venular BM contains pre-formed regions with low expression of certain BM components, denominated Low expression regions (LER), which are preferentially utilized by transmigrating neutrophils and monocytes [29, 40]. Alignment of these regions with gaps between adjacent pericytes suggests a key role for these cells in vascular BM generation *in vivo*. Vascular BM architecture depends on the migration of neutrophils, but not monocytes, through the LER remodeling these regions and increasing their size [41, 42], suggesting the involvement of proteases in this response.

6. Neutrophil polarization and migration structures

Neutrophils present in the blood are able to tissue-injury or infection signals by adhering to vascular endothelial cells, then transmigrating across the endothelium through the basement membrane and homing into sites of infection or inflammation.

The following four steps mediate the multiple cycles of attachment and detachment generating neutrophil forward movement during migration: the leading edge protrudes one or several pseudopods by actin flow; protruding membrane and surface receptors interact with the substrate; actomyosin-mediated contraction of the cell body occurs in mid-region, thus the rear of the cell moves forward. Neutrophil migration moves at up to 30 μm/min, lacks strong adhesive interactions to the tissue, and commonly preserves tissue integrity [9].

Receptors such as β2 integrins in neutrophils show discrete relocation toward the tips of ruffles [43]. The mid-region of amoeboid cells contains the nucleus and a relatively immobile cell region that maintains the front-rear axis. The trailing edge contains the highly glycosylated surface receptors CD43 and CD44, adhesion receptors including Intercellular adhesion molecule (ICAM)-1, ICAM-3, β1 integrins, and Ezrin-radixin-moesin adaptor proteins (ERM), as well as GM-1-type cholesterol-rich microdomains [44]. The uropod mediates cell–matrix and cell–cell interactions during migration and has a putative anchoring function [45]. The uropod extends rearward from the nucleus and contains the microtubule-organizing center and rearward-polarized microtubules, the Golgi, and abundant actin-binding ERM proteins. In association with microtubules, mitochondria localize to the rear of the cell that, presumably, due to local ATP delivery to the region of ATP-dependent actomyosin contraction, is required for proper polarization, uropod retraction, and migration [10, 46].

7. Polarization of cytoskeletal and signaling scaffolds

In neutrophils, polarization and migration to chemoattractant gradients such as chemokines and cytokines, lipid mediators, bacterial factors, and Extracellular matrix (ECM) degradation products including collagen, fibronectin, and elastin fragments [47, 48], is known as chemotaxis. After chemokines and chemoattractants bind to the extracellular domains of their cognate G protein-coupled receptor (GPCRs) pseudo- and lamellipodia protrusion are induced. In leukocytes, the majority of GPCRs transmit through the α subunit of Giα. These GPCR include the following: the fMLP (N-formyl-Met-Leu-Phe) receptor and the C5a receptor; chemokine receptors including CCR7, CXCR4, CXCR5, and CCR3; the leukotriene B4 receptor BLT1; sphingosine-1-phosphate receptors 1–4 (S1P1–4), and Lysophosphatidic acid (LPA) receptors 1–3 [49]. All these GPCR mediate promigratory signals but also enhance cell activation. A key GPCR-mediated pathway is signaling through the Phosphatidylinositol-3-kinase (PI(3)K), which contains the p110γ catalytic subunit). PI(3)K-γ is recruited into the inner leaflet of the plasma membrane by the G protein βγ subunit, where it becomes activated and subsequently phosphorylates Phosphatidylinositol phosphates (PIP) and other effectors [50]. PIP serve as docking sites for pleckstrin-homology domain-containing proteins, notably Akt (also known as protein kinase B), which is implicated in inducing actin polymerization and pseudopod protrusion by phosphorylating downstream effectors [51] such as the actin-binding protein girdin [52]. A second pathway linked with PI(3)K activation is induced by ζ-chain-associated receptors, including T cell receptors (TCRs) and receptors FC (FcRs). These receptors signal through tyrosine kinases Lck and Zap-70 to class Ia PI(3)Ks (consisting of p110δ) and activate downstream Akt, as well as the GTPases Rac and Cdc42 [53]. A third, PI(3)K-independent pathway induced by the fMLP receptor in neutrophils leads to the activation of p38 mitogen-associated protein kinase and downstream Rac activation [54, 55]. Ultimately, Rac

induces actin polymerization through WAVE (Scar) and Arp2/3. WAVE, a member of the WASP family of actin-binding proteins, mediates actin filament formation [56], while Arp2/3 causes sideward branching of actin filaments. Together, these activities generate interconnected, branched networks [57]. Thus, promigratory signals received at the leading edge generate local Rac activation and actin network protrusion, pushing the plasma membrane outward. Preferential receptor-sensitivity mechanisms at the leading edge are likely diverse and may include local signal- amplification mechanisms [58] and exclusion of counter-regulatory proteins. The mid-region generates actomyosin-based stiffness and contractility, limits lateral protrusions, and thereby maintains a stable, bipolar cortex. The cytoskeletal motor protein myosin II, located in the central and rear regions of leukocytes, promotes actin-filament contraction and limits lateral protrusions. Myosin II cross-links actin filaments in parallel, forming the contractile shell required to hold the extending cell together and propelling the cell nucleus, the most rigid part of the cell, forward [59].

8. Leukocyte movement in different environments and initial migration

Neutrophils are able to migrate along or through 2- or 3- dimensional (2-D or 3-D) surfaces. 2-D Surfaces, such as inner vessel walls, peritoneum, and pleura, require integrin-mediated attachment known as haptokinesis and polarized adhesion through binding of integrins α4β1 and LFA-1 (αLβ2) to their counterparts (VCAM-1 and ICAM-1)(Figure 3A). In contrast, migration in 3-D, ECM environments, which are composed mainly of cellular (lymph node) or fibrillar ECM components, is integrin-independent and cells use weakly adhesive-to-nonadhesive interaction and traction mechanisms that are mediated by actin flow along the confining ECM scaffold structure, contributing to shape change and squeezing [9, 44, 60] (Figure 3B). It is likely that neutrophils adapt to tissue geometry and follow paths of least resistance, a process known as contact guidance (Figure 2).

For passage, the first postendothelial tissue structure and barrier to cells undergoing diapedesis, locally confined cleavage of the structural proteins laminin-10 and type IV collagen, occurs by secreted or membrane-anchored Matrix metalloproteases (MMPs) and serine proteases [61, 62]. Cell-body deformation is coupled with cytoplasmic propulsion and streaming through preexisting or newly formed pores; the deformation and constriction capability of leukocytes is considerable, especially for neutrophils [63].

Interestingly, a recent study showed the existence of venule-wall regions in which laminin-10, collagen IV, and nidogen-2 expression is considerably diminished; neutrophil transmigration enlarges the size of these regions, and their protein content is further reduced, an effect that appears to involve neutrophil-derived serine proteases [40]. Location of proteases at the leukocyte cell surface takes place through two different mechanisms: either by endogenous expression as transmembrane proteins or by binding of extracellular proteases to integral membrane receptors. Integrins are shown to act as anchoring receptors for several proteases including MMPs; such interactions have been detected in caveolae, invadopodia, and at the leading edge of migrating cells, where directed proteolytic activity is required [64]. In this regard, pro-MMP-2 and pro-MMP-9 are bound to αLβ2 and αMβ2 on the surface of activated leukemic cells, and inhibition of these complexes blocks β2 integrin-dependent leukocyte migration [65]. Pro-MMP-9– αMβ2 complexes are primarily localized into intracellular granules of resting neutrophils, but after cellular activation, they are

relocalized to the cell surface [66]. Neutrophils secrete laminin, suggesting that leukocyte-derived matrix proteins might also contribute to the transmigration process [67].

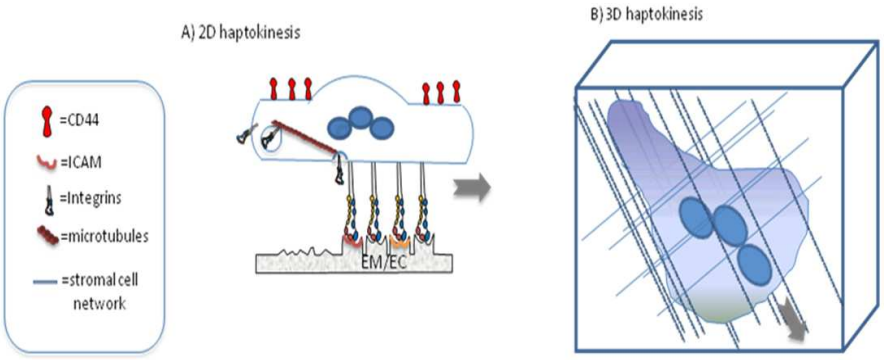

Fig. 3. Type-substrate interaction with neutrophils. A) Two-dimensional integrin-mediated neutrophil migration. *In vivo* 2-D haptokinetic migration is present during crawling on Endothelial cell (EC) or through Extracellular matrix (EM). B) Three-dimensional integrin-independent neutrophil migration. *In vivo*, this occurs through organized tissue structures.

9. Role of cytoskeleton in regulating integrin adhesiveness

Integrins are a superfamily of heterodimeric cell-surface receptors that are found in a broad range of animal species [68]; their main role, as their name implies, is to integrate the cell cytoskeleton with adhesion points of extracellular matrix and cell-surface ligands in order to mediate essential cellular processes such as cell-cell and cell-extracellular matrix interactions, polarization in response to extracellular cues, cell migration, differentiation, survival, and cell-pathogen interactions [69].

In vertebrates, 19 different integrin α subunits and eight different integrin β subunits have been reported, in combination forming about 25 αβ heterodimers [70]. The majority of α/β-subunit combinations can be organized into three fundamental groups based on subunit type (β1, β2, and β3, or αv chains, on the extracellular matrix protein-type recognized, or on the specific adhesion motifs [71] (Table 1).

β1 integrins form the first and largest group of integrins and are ubiquitously distributed in nucleated cells as well as in platelets. β1 Integrins are expressed in bone marrow-derived cells (except for neutrophils), in certain tumor cells, and in muscle development. A second major group of integrins shares either the β3 or the αv subunit (Table 1) and recognizes different ligands from a broad gamma of cell and tissue sources. Integrins with the αv subunit may form dimers with at least five different β chains, including the β1 chain. Subunits αv and β3 recognize Arg-Gly-Asp (RGD) domains present in extracellular matrix proteins.

The third group of integrins shares the β2 integrin chain, whose expression is restricted to leukocytes [72] (Table 1). Receptors such as α4β2, also known as the LFA-1 integrin, determine the capability of leukocytes in endothelial epithelium transmigration and recognize members of the Intercellular adhesion molecule (ICAM) family of adhesion proteins. In contrast, expression of αMβ2 is restricted to monocytes, macrophages, and granulocytes; it recognizes

	Ligands	Motifs	Distribution
β1 integrin			
α1β1	*Co1,Lm*	ND	*EC, SMC, TC, Monos*
α2β1	*Col, Fn, Lm, Echovirus 1*	*DGEA*	*Plt, EC, Fb, SMC, TC, EPC*
α3β1	*Col, Epiligrin, Fn, Lm, Invasin*	*RGD*	*EC, TC, EPC, Fb*
α4β1	Fn, Invasin, VCAM-1	EILDV (Fn) *QIDSPL(VCAM-1)*	TC, Monos, Eos, LC, ER
α5β1	Fn, Invasin	RGD	Fb, EC, Monos, TC, Plt
α6β1	Lm, Invasin	ND	Plts, TC, EC, EPC
α7β1	Lm	ND	Myocytes
α8β1		ND	*SMC*
α9β1	Col, Lm, Tenascin	RGD	EPC, Myocytes
αϖβ1	Fn,Vn	RGD	Fb
αv and β3 integrins			
αvβ1	Fn, Vn	RGD	Fb
αvβ5	Vn, HIV Tat, Adenovirus	RGD	EC, EPC, Fb, Tumors
αvβ6	Fn, Tenascin	RGD	
αvβ3	Vn	RGD	Melanoma
αvβ3	Col, Fib, Fn, Lm Opn, Pn, TSP, Vn	RGD	EC, FB, Monos, SMC, OC
	vWf, HIV Tat, Tenascin, Adenovirus		Plt, Tumors
αIIbβ3	Col, Fib, Fn, TSP, Vn, vWf, *Borrelia*	KQAGDV	Plt, Mega
αRβ3	Fib, Fn, Vn, vWf	RGD	PMN
β2 integrin			
αLβ2	ICAMs (1-3)	ND	TC, BC, LGL, Monos, PMN, Eos
αMβ2	Fib, Fn, Factor X, ICAM-1, iC3b		PMN, Monos, Macros, LGL
αχβ2	Fib, iC3b	GPRP	Monos, Macros, PMN
αΔβ2		ND	TC. Macros
Other integrins			
α6β4	Lm	ND	EC, EPC, Schwann cells
α4β7	Fn, MAdCAM, VCAM-1	EILDV (Fn)	Gut homing, TC
αEβ7	E-Cadherin	ND	Epithelial TC

Table 1. Classification of integrins according to ligand motifs and distribution.
Abbreviations: BC = B cells; Col = Collagen; EC = Endothelial cells; Eos = Eosinophils; EPC = Epithelial cells; Fb = Fibroblasts; Fib = Fibrinogen; Fn = Fibronectin; iC3b = inactivated component of complement; Lm = Laminin; LGL = Large granular lymphocytes; Macros = Macrophages; Mega = Megakaryocytes; Monos = Monocytes; OPN = Osteopontin; Plt = Platelets; PMN = Neutrophils or Polymorphonuclear leukocytes; SMC = Smooth muscle cells; TC = T cells; TSP = Thrombospondin; Vn = Vitronectin; vWf = von Willebrand disease. (Modified from [71]).

fibrinogen and inactivated C3b, playing an important role in the phagocytosis of opsonized particles and bacteria [73]. The fourth group of integrins includes three integrins (α6β4, α4β7, and αEβ7); these integrins recognize extracellular matrix components as well as adhesion molecules of the Immunoglobulin superfamily (IgSF). Common integrins expressed on leukocytes and their counterparts are summarized in Table 1.

Association of extended forms of integrins with the cortical cytoskeleton is required to integrate mechanical forces from shear flow and F-actin and to undergo ligand-induced strengthening at endothelial contacts. Key differences between α4 and β2 integrins regarding their increase in cytoskeleton-mediated avidity may occur. The α4 integrins can bind paxillin upon dephosphorylation of Ser988 in their cytoplasmic domain at the sides and rear pole of the cell, whereas PKA-mediated phosphorylation of these integrins is confined to the cell's leading edge. Paxillin regulates α4 integrin function (tethering and firm adhesion) [74], enhancing their migration rate and reducing their spreading, and paxillin–α4 interaction downregulates the formation of focal adhesions, stress fibers, and lamellipodia by triggering activation of different tyrosine kinases, such as Focal adhesion kinase (FAK), Pyk2, Src, and Abl [75, 76]. The α4–paxillin complex inhibits stable lamellipodia by recruiting an ADP-ribosylation factor (Arf)-GTPase-activating protein that decreases Arf activity, thereby inhibiting Rac, and limiting lamellipodia formation to the cell front [77]. Recently, it was discovered that integrins can induce PIP5K1C-90 polarization independently of chemoattractants. This integrin-induced PIP5K1C-90 polarization works together with chemoattractant signaling in regulating neutrophil polarization and directionality *in vitro* and infiltration *in vivo* [78].

It has been described that LFA-1 and Mac-1 may use adapter molecules talin, α-actinin, filamin, and 14-3-3 to anchor to the actin cytoskeleton properly [79, 80]. Regarding subcellular localization, LFA-1 pattern ranges from low- in the lamellipodia to high expression in the uropod. However, it has been reported that high-affinity clustered LFA-1 is restricted to a mid-cell zone, termed the "focal zone", different from focal adhesions and focal contacts. In addition, talin, properly activated by phosphorylation or by phosphatidylinositol-4,5-bisphosphate (PIP2), is essential for formation and stability of the focal zone and for LFA-1-dependent migration [81].

Locomotion can be regulated by integrins because the signals involved in integrin-mediated leukocyte firm adhesion to endothelium are subsequently attenuated to allow leukocyte migration toward an appropriate transmigration site. β2 integrins appear to promote direct locomotion, success in correct positioning at the endothelial junction, and effective diapedesis [82, 83]. Upon interaction with their ligands, integrins activate distinct myosin-contractility effectors, actin-remodeling GTPases, and molecules involved in microtubule-network regulation at motile leukocyte leading and trailing edges [84]. During cell polarization, Cdc42, Myosin light chain kinase (MLCK), Rac, RapL, Rap1, mDia, myosin-IIA, and chemokine receptors are redistributed to the cellular front, participating in exploratory filopodia formation and in lamellipodia extension. In contrast, Rho- and Rho-associated kinase (ROCK) (both involved in trailing- edge retraction), the Microtubule-organizing center (MTOC), and adhesion receptors ICAM-1, ICAM-3, CD44, and CD43 move toward the rear pole [85].

Recently, dystrophin protein-adhesion complex proteins such as short dystrophins, utrophins, and the dystrophin-associated protein complex (α-dystroglycan, α–syntrophin and α–dystrobrevins) form part of actin-based structures such as lamellipodia and uropod, in which their polarized distribution is evident and their feasible role in chemotaxis and migration is strongly suggested [86].

Other proteins with differential distribution appear in Figure 4 and the list is increasing.

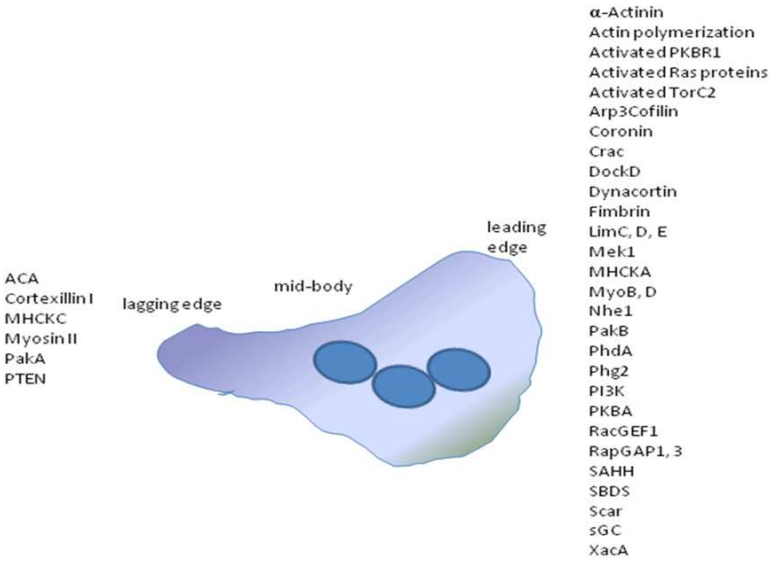

Fig. 4. Neutrophil regions observed after triggered activation and differential protein distribution. Adapted from [87].

10. Conclusions

For exiting the vasculature, leukocytes follow a consecutive sequence of events that starts with the first contact of free-flowing neutrophil to the vascular endothelium followed by leukocyte rolling along the vessel wall. Both events are mediated by specialized receptor ligand pairs consisting of a member of the selectin family of adhesion molecules and specific carbohydrate determinants on selectin ligands. During rolling, leukocytes are in intimate contact with the vascular endothelium, enabling endothelial-bound chemokines to interact with their respective chemokine receptors on the neutrophil surface. Upon binding to the receptor, chemokine receptor-mediated signaling events trigger the activation of β2 integrins. Activated integrins subsequently interact with endothelium-expressed ligands, which lead to a reduction in leukocyte rolling velocity and eventually, to mediate stable adhesion and migration across the blood vessel wall. Following neutrophil spreading and intravascular crawling along the endothelium, tethered neutrophils reach the correct spot for exiting into tissue. Upon neutrophil stimulation, actin, which is one of the major components of the cytoskeleton in neutrophils, is reorganized through reversible cycles of polymerization and depolymerization, thereby comprising the driving motor for the

formation of lamellipodia and pseudopodia during migration and phagocytosis. Activated neutrophils become polarized with a contracted tail (uropod) in the rear and F-actin-rich protrusions at the front and start crawling. Actin and the proteins regulating actin polymerization are key players in the establishment of morphological and functional cell polarity. Actin polymerization and membrane ruffling comprise the first events leading to the establishment of chemoattractant-stimulated neutrophil polarization.

Morphological changes imply cytoskeleton redistribution triggered by certain activated pathways which are spatiotemporally coordinated.

Undesrtanding the molecular and cellular interactions that regulate neutrophil transmigration could be of great value to design novel therapeutic strategies directed to promote or suppress an inflammatory response, which may be of potential benefit under physiological or pathological circumstances.

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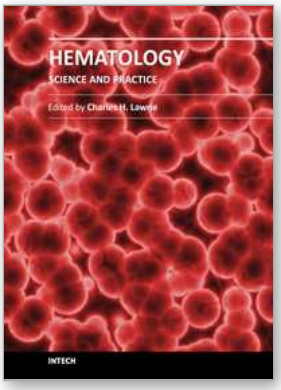

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Hematology encompasses the physiology and pathology of blood and of the blood-forming organs. In common with other areas of medicine, the pace of change in hematology has been breathtaking over recent years. There are now many treatment options available to the modern hematologist and, happily, a greatly improved outlook for the vast majority of patients with blood disorders and malignancies. Improvements in the clinic reflect, and in many respects are driven by, advances in our scientific understanding of hematological processes under both normal and disease conditions. Hematology - Science and Practice consists of a selection of essays which aim to inform both specialist and non-specialist readers about some of the latest advances in hematology, in both laboratory and clinic.

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