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Review

Leukocyte Migration into Inflamed Tissues

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Leukocyte migration through activated venular walls is a fundamental immune response that is prerequisite to the entry of effector cells such as neutrophils, monocytes, and effector T cells to sites of infection, injury, and stress within the interstitium. Stimulation of leukocytes is instrumental in this process with enhanced temporally controlled leukocyte adhesiveness and shape-changes promoting leukocyte attachment to the inner wall of blood vessels under hydrodynamic forces. This initiates polarized motility of leukocytes within and through venular walls and transient barrier disruption facilitated sequentially by stimulated vascular cells, i.e., endothelial cells and their associated pericytes. Perivascular cells such as macrophages and mast cells that act as tissue inflammatory sentinels can also directly and indirectly regulate the exit of leukocytes from the vascular lumen. In this review, we discuss current knowledge and open questions regarding the mechanisms involved in the interactions of different effector leukocytes with peripheral vessels in extralymphoid organs.

INTRODUCTION

Circulating blood leukocytes are required to migrate to sites of tissue injury and infection with the principal aim of eliminating the primary inflammatory trigger and contributing to tissue repair. In innate immunity, this process is largely initiated by pathogen-associated molecular patterns (PAMPs), released by invading microorganisms, and damage-associated molecular patterns (DAMPs), derived from damaged and/or dead-cells, or in response to tissue and/or cellular stress (Medzhitov, 2008). In addition, antigens, largely through activation of resident memory T cells, can trigger recruitment of leukocytes via secretion of various primary inflammatory cytokines. Tissue sentinel cells, including mast cells, macrophages, and dendritic cells (DCs), play a key role in detection of such danger signals and can release a wide range of proinflammatory mediators to promote leukocyte recruitment.

The primary step in leukocyte migration is the establishment of weak and transient adhesive interactions between leukocytes and endothelial cells of postcapillary venular walls in close vicinity to inflamed tissues (Figure 1). This facilitates in situ stimulation of leukocytes by endothelial presented chemoattractants displayed on the luminal side of blood vessels, propagating firm leukocyte arrest, adhesion strengthening, crawling, and subsequently migration of cells out of the blood vasculature (reviewed by [Ley et al., 2007]). This series of sequential but overlapping steps termed the leukocyte-adhesion cascade, is primarily mediated by two major adhesion receptor families, selectins (expressed on leukocytes and endothelial cells) and integrins (leukocytes) (reviewed by [Ley et al., 2007]) (Figure 1). Activation of endothelial cells is a decisive step in this process and can occur in a rapid and protein-synthesis-independent manner (within minutes) resulting in cell-surface expression of preformed adhesion molecules involved in initiating rapid attachment of leukocytes to blood vessels (e.g., P-selectin). In addition, endothelial cell activation can occur more slowly (within hours) and involve transcriptional induction of numerous leukocyte-trafficking molecules (primarily endothelial cell selectins, integrin ligands, and de novo transcribed chemoattractants [reviewed by Pober and Sessa, 2007]). Rapid activation of endothelial cells can be induced by inflammatory stimuli such as histamine and PAF while slow activation can be driven by cytokines (e.g., interleukin-1β [IL-1β] and tumor necrosis factor [TNF]). These modes of endothelial cell stimulation have been termed type I and type II activation, respectively (Pober and Sessa, 2007). Shortly after arresting on their target blood vessel endothelial cells, leukocytes must integrate additional chemotactic cues—primarily chemokines or lipid chemoattractants (reviewed by [Alon and Shulman, 2011; Rot and von Andrian, 2004]). These cues govern the site and route of leukocyte migration along and through the endothelial cell barrier, determining a potential need for chemotactic crawling on the apical aspect of the endothelium to seek permissive sites and/or additional exit cues. The latter is supported by the ability of leukocytes to extend ventral protrusions through junctions between adjacent endothelial cells or into the endothelial cell body, facilitating a sensing mechanism for detection of chemotactic gradients associated with the endothelium or in the subendothelial cell space.

Beyond the endothelium, leukocytes are required to traverse through the pericyte layer embedded within the venular basement membrane, a phase of leukocyte trafficking that can also involve leukocyte sensitization by tissue-derived inflammatory signals (Figure 1). The collective breaching of the venular wall is a highly instructive process during which the transmigrating leukocytes and both cellular and matrix components of the vasculature undergo extensive alterations via spatially coordinated bidirectional signaling events details of which have begun to unfold (reviewed by [Nourshargh et al., 2010]). Most notably, transmigrated leukocytes exhibit altered phenotype, enhanced survival, and increased effector functions, such as greater ability

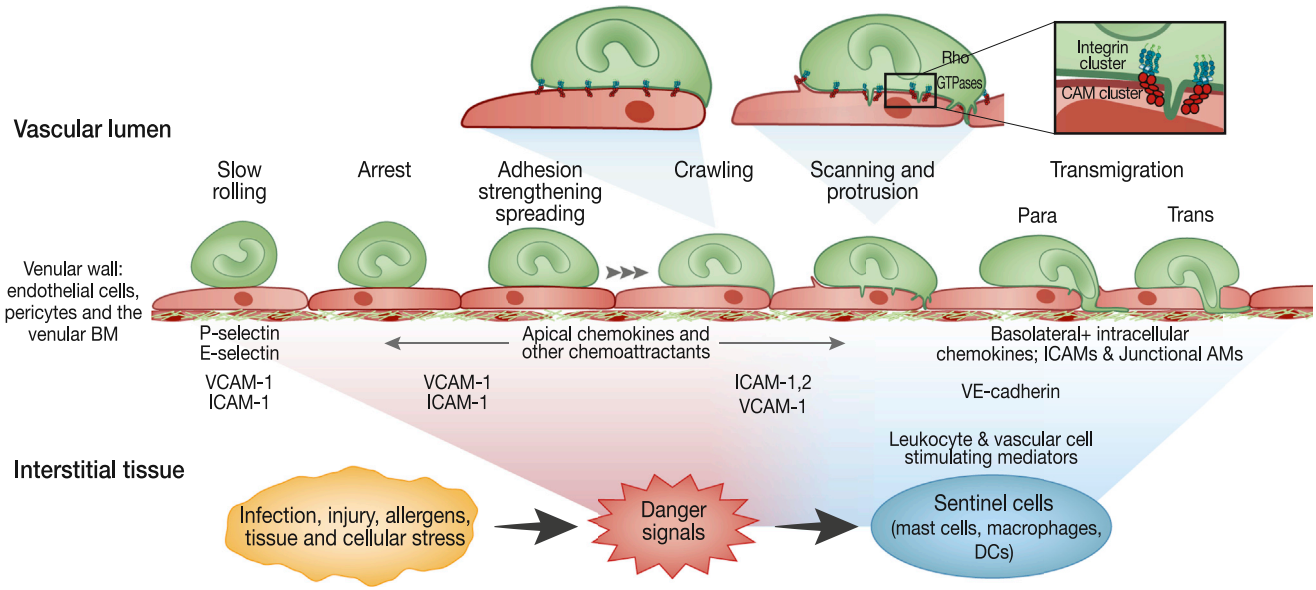

Figure 1. Leukocyte-Vessel Wall Interactions

In response to a diverse range of proinflammatory triggers, released danger signals and other proinflammatory mediators can stimulate leukocytes and vascular cells to initiate a cascade of leukocyte adhesion and motility responses on the luminal aspect of venular endothelial cells. This enables optimal scanning of the vascular lumen for exit signals. Leukocyte rolling, firm attachment, and intravascular crawling are sequentially mediated by the indicated endothelial cell adhesion molecules and leukocyte endothelial selectin and integrin ligands, responses that are prerequisites to leukocyte migration through venular walls. A delicate balance between integrin-ligand microclusters and actomyosin machineries (inset) allows arrested leukocytes to scan the endothelial lumen for chemotactic exit signals under hydrodynamic forces. This balance is spatially and temporally regulated by multiple GTPases activated primarily by chemoattractant signals. For simplicity, initial capturing and fast rolling steps are omitted. More details of the molecular interactions are provided in the text and in Box 1. BM, basement membrane.

to kill and clear invading pathogens and tumor cells. Consequently, breaching of venular walls not only provides a regulated process for facilitating leukocyte migration into inflamed tissues but also acts as a key process through which tissue-infiltrated leukocytes are primed for delivering an effective immune response (Nourshargh et al., 2010; Stark et al., 2013). Once in the interstitial tissue, leukocytes can exhibit multiple forms of leukocyte migration patterns where numerous cellular and molecular regulatory mechanisms have been proposed (Lämmermann and Germain, 2014; McDonald and Kubes, 2011; Weninger et al., 2014). This review will provide a brief outline of recent advances in our current knowledge of the bidirectional interactions of effector leukocytes with different vascular beds followed by a more in-depth discussion of the mechanisms that regulate leukocyte breaching of postcapillary venules in nonlymphoid tissues.

Luminal Leukocyte-Vessel Wall Interactions in Postcapillary Venules

Within the leukocyte-adhesion cascade, each step is conditional on the next (Figure 1) and multiple molecular choices at each step provide a large combinatorial diversity and high specificity required for selective leukocyte recruitment at the right tissue and within the correct context (reviewed by [Ley et al., 2007]). Integrins constitute a family of about 30 heterodimers that participate in a wide spectrum of cellular functions and whose ligand-binding activity is rapidly regulated by cytoskeletally controlled conformational changes and mechanical forces, as well as by redistribution from intracellular pools (Herter and Zarbock, 2013). With the exception of effector lymphocytes and certain monocyte subsets that express adhesive integrins (Carlin et al., 2013; Lek et al., 2013; Shulman et al., 2012), all circulating leukocytes maintain their integrins in largely inactive states. Leukocyte integrins must develop high affinity and avidity for their specific endothelial ligands in order to establish firm shear-resistant adhesions (Alon and Dustin, 2007; Carman and Springer, 2003; Ley et al., 2007). This transition requires freely flowing leukocytes to be reversibly captured on the endothelium, a step that is mediated by leukocyte glycoprotein (e.g., PSGL-1) interactions with members of the selectin family P- and E-selectin. Selectins can be induced on acutely or chronically stimulated postcapillary venules (e.g., P-selectin and P- and E-selectin, respectively), as well as on platelets or platelet microparticles deposited on injured blood vessels (reviewed by [Ley et al., 2007; Zarbock et al., 2011]). Free-flowing leukocytes can also interact with attached leukocytes through binding of leukocyte L-selectin to leukocyte PSGL-1 (Walcheck et al., 1996).

Selectin-mediated leukocyte rolling is often stabilized by leukocyte microvilli flattening that slows down the rolling leukocyte and further enhances the topographical availability of its chemokine receptors and integrins for interactions with their respective endothelial ligands (Chen and Springer, 1999). This response is further supported by elongation of rear tethers as well as by cell autonomous adhesive substrates termed slings (Sundd et al., 2012). These rolling interactions increase the efficiency of leukocyte encounters with endothelial cell-expressed chemoattractants (largely chemokines) and