Editorial

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Myeloid Cells in Traffic

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Appearance of neutrophils and monocytes at the site of inflammation is a hallmark event during the inflammatory response. Trafficking of different leukocyte subsets requires a coordinated interaction of a variety of molecules in a process known as the leukocyte recruitment cascade. Classical descriptions of this multistep process consisted of leukocyte rolling, activation, adhesion and subsequent transmigration, involving selectins, cell adhesion molecules and chemokines as well as their respective receptors [1]. However, in recent years, this recruitment cascade has been refined by implementation of intermediate steps (e.g., adhesion strengthening and intraluminal crawling), discovery of tissue- (e.g., in liver, lungs and large arteries) and leukocyte-specific (e.g., for classical vs. nonclassical monocytes) recruitment mechanisms, as well as by recognition of intercellular interactions (e.g., between leukocyte subsets). This special issue accommodates all these new developments in several review articles.

Neutrophil homeostasis is maintained by a fine balance between granulopoiesis, retention in and release from the bone marrow as well as by clearance and destruction. Chemokine axes involving CXCR4 and CXCR2 are critically involved in the retention, mobilization and homing of neutrophils at sites of granulopoiesis [2, 3]. The importance of these axes in regulating myeloid cell homeostasis was shown under physiological conditions such as circadian changes [4] but also under inflammatory conditions where disturbance of these axes induces increases in circulating myeloid cells and worsening of inflammatory diseases [5, 6]. The molecular mechanisms underlying the control of neutrophil homeostasis in steady-state and inflammatory conditions are reviewed in detail by Strydom and Rankin [7].

Neutrophils are the first leukocyte subset recruited to sites of inflammation. In the absence of microbial stimuli, i.e. in sterile inflammation, damage-associated molecular patterns (DAMPs) represent the trigger for neutrophil emigration. Important DAMPs are extracellular ATP [8, 9], mitochondrial formylated peptides [10] and DNA [11], all of which are released by dying cells. Here, Pittman and Kubes [12] summarize mechanisms by which DAMPs set off the neutrophil recruitment cascade in sterile inflammation. Once activated and adherent to the endothelium, neutrophils need to breach the endothelial barrier to reach the inflammatory site. Intercellular junctions connecting individual endothelial cells form a tight barrier, thus making paracellular transmigration a highly regulated process. This process is complemented by emerging alternative routes of transmigration such as transcellular migration and reverse transmigration [13]. Here, Daniel and van Buul [14] summarize the molecular mechanisms that regulate endothelial cell-cell junctions and prevent or permit leukocyte transendothelial migra-

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tion. Recent findings have illustrated that beyond the vascular lumen, the breaching of the venular wall can also involve an analogous cascade of adhesive events. For neutrophils, this involves a tightly regulated and sequential series of responses within venular walls, initiating with adhesive steps that guide neutrophils through endothelial cells lining the venular wall, followed by responses that mediate and regulate their migration through the pericyte sheath and the venular basement membrane [15]. The review by Voisin and Nourshargh [16] provides a detailed summary of the emerging adhesive cascade of neutrophils within venular walls, thus illustrating the complexities of neutrophil transmigration.

Based on the use of in vivo model systems, we have a good understanding of the basic principles of the classical recruitment cascade. While this commonly agreed paradigm might be applicable to most peripheral tissues, recruitment mechanisms may substantially vary in different organs, such as the lung [17, 18], liver [19, 20] and kidney [21, 22]. These organs are highly specialized tissues with unique cell populations and structural organization, which enables them to fulfill their individual functions. The review of Rossaint and Zarbock [23] highlights current concepts of tissue-specific differences. The recruitment cascade receives another level of complexity when changing the focus towards chronic inflammatory processes such as atherosclerosis. There, it has been shown that neutrophils employ a different set of chemokine receptors to enter atherosclerotic lesions when compared to sites of microvascular inflammation [6]. This is based on the endothelial deposition of platelet-derived chemokines which attract neutrophils and monocytes alike [5, 6]. In addition, neutrophils may pave the way for arterial infiltration of classical monocytes [24]. In this issue, Drechsler and Soehnlein [25] highlight the promiscuous pathways by which classical monocytes enter atherosclerotic lesions.

Once neutrophils, classical monocytes and macrophages have entered the site of injury or infection, they collaborate to remove foreign entities. After the inflammatory stimulus has been eliminated, the ongoing inflammatory response must be resolved to avoid excessive tissue damage and to initiate the return to tissue homeostasis in a process termed 'resolution' [26]. During the resolution of inflammation, a set of brakes prevents further infiltration of inflammatory cells and, interestingly, various mediators cooperate herein. Annexin A1, lipoxin A4 and resolvin D1, all of which act via the same receptor, namely FPR2, join forces to abrogate leukocyte recruitment, thus laying the ground for resolution of inflammation [27–29]. The review presented by Norling and Perretti [30] focuses on the mediators, targets and pathways orchestrating leukocyte trafficking during resolution. Neutrophil apoptosis is a crucial event during resolution of inflammation linking to reduced leukocyte recruitment and reprogramming of macrophages. In an original article, Christenson et al. [31] demonstrate the importance of autocrine interleukin-1β signaling of emigrated neutrophils in the regulation of their apoptosis.

Neutrophil and monocyte tissue infiltration are hallmark events during inflammation and offer various means of therapeutic interference. A detailed understanding of these processes in the various forms of inflammation (acute vs. chronic, sterile vs. microbial, macro- vs. microcirculation, different vascular beds) will allow for the tailoring of specific strategies to target the complex faces of inflammation.

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