Chemokines take centre stage in vascular biology

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The trafficking and extravasation of leukocytes during immune surveillance and inflammation is governed by the chemokine family of small chemotactic peptides. The structural classification of chemokines, their cognate heptahelical receptors, expression patterns and biological functions in immune cell regulation during health and disease have been critically reviewed (1–4). It has been proposed that the abundance of chemokines in inflammatory scenarios imparts a considerable degree of redundancy but also robustness to the regulatory system (5, 6). Recently, the concept of a functional chemokine ‘interactome’ constituted by the molecular interactions of different chemokines may provide a context-related vocabulary to finely tune local immune cell responses in a specific inflammatory milieu, further expanding the plasticity of the regulatory chemokine network (6). The role of chemokines in vascular biology was first appreciated through their expression in atherosclerosis and their involvement in mononuclear cell recruitment during vascular disease, which is characterized by an intriguing level of specialization and cooperation at distinct steps of the extravasation cascade and for different mononuclear cell subtypes (7). Beyond their functions in primary atherosclerosis, chemokines contribute to remodelling and neointima formation in response to different forms of vascular injury, to atherothrombotic complications, to the course of myocardial infarction and tissue damage, and to angiogenesis and neovascularization (4, 7, 8). Thus, it is fair to conclude that chemokines have taken major roles in different performances on the stage of vascular biology, which warrants a closer look at various aspects (Fig. 1) in the forum of this theme issue on Thrombosis and Haemostasis.

To set the stage, the fundamental mechanisms of chemokine transport, presentation and clearance with emphasis to their functional relevance for the actions of chemokines in vivo will be summarized in an article by Colditz et al. (9). Whereas the induction of leukocyte transmigration by chemokines in vitro has been extensively studied in reductionist models, the extravasation of leukocytes from the circulation in response to chemokines at the endothelial interface in vivo is regulated by interactions with accessory molecules (e.g. interceptors, glycosaminoglycans, and enzymes) affecting their immobilisation, transport and degradation. These mechanisms are crucial for controlling the localization and timing of chemokine activities in vivo.

A special case of chemokines and their role in vascular inflammation is highlighted in an article by Ludwig and Weber (10). As transmembrane molecules on the surface of endothelial cells, the chemokines CX3CL1 and CXCL16 can interact with their receptors CX3CR1 and CXCR6, respectively, on leukocytes to mediate shear-resistant adhesion. Cleavage by ADAM family metallopeptases can result in cell detachment and chemotactic activity, while their up-regulation in atherosclerosis may serve recruitment functions, but in case of CXCL16 may also promote uptake of oxidized LDL as a scavenger receptor. This may explain differential effects in atherogenesis, where CX3CL1 promotes, while CXCL16 protects against lesion formation.

Besides a role in haemostasis, mediated by activation and aggregation, platelets constitute a crucial force driving vascular disease, e.g. atherosclerosis. The article by von Hundelshausen et al. (11) highlights the contribution of chemokines and their precursors released from platelets, namely CTAP-II, its truncation product CXCL7, PF4 (CXCL4), its variant PF4alt (CXCL4L1) or RANTES (CCL5) in atherogenesis and angiogenesis. The relevance of these platelet-derived chemokines, alone or in cooperation, and of regulatory mechanisms, such as proteoglycan binding, proteolytic processing, and formation of homo- or hetero-oligomers, will be discussed.

As the primary cause of heart disease and stroke, atherosclerosis is widely considered a chronic inflammatory disease characterized by a dysbalanced recruitment of pro-inflammatory cells, e.g. monocytes, and anti-inflammatory immune cells, e.g. protective regulatory T cells, into the intima (12). How this is controlled by chemokines and their receptors, and the therapeutic potential of blocking their functional interactions in atherosclerosis, is the topic of the article by Braunerreuther et al. (13). Two major monocyte subsets with differential expression of CCR2, CX3CR1 and CCR5 have been identified, which may affect the patterns of their recruitment and activities in plaques or in post-ischemic infiltration. The CCR2/CX3CR1high monocytes are less frequently recruited em-
ploying CCR5 and preferentially acquire the dendritic marker CD11c, while classical CCR2+ monocytes use CX3CR1 (14, 15). This implies combined targeting of CCR5 and CX3CR1 during atherogenesis, while acute inflammatory responses may depend on CCR2.

As a major complication of atherosclerosis, instability and rupture of inflammatory plaques can lead to a thrombotic occlusion of the diseased artery. Emerging evidence obtained in mouse models unveiled a role of chemokines as important modulators of thrombus formation especially in the context of atherosclerosis. This will be discussed in an article by Lamberte et al. (16) with regards to the effects of platelet-derived chemokines, which can support or inhibit inflammatory thrombosis and platelet activation, laying the premises for future investigations in this area.

As a consequence of arterial injury, e.g. by therapeutic revascularization of stenosed or thrombosed arteries or due to transplant arteriopathy, the responses of the vessel wall termed remodelling include neointimal hyperplasia, inflammation, medial thickening, and endothelial dysfunction. The complex network of chemokines and their receptors involved at different steps of these processes is reviewed by Schober and Zernecke (17). While CCL2/CCR2 and CCL5/CCR5 contribute to monocyte infiltration and can stimulate smooth muscle cell proliferation, the chemokine CXCL12 and its receptor CXCR4 are instrumental in neointimal recruitment of smooth muscle cell progenitor cells, and CXCL1/7 with their receptor CXCR2 mediate endothelial recovery and recruitment of endothelial progenitor cells. This may be particularly relevant for therapeutic interventions.

Evidence for the importance of chemokine signaling in the post-ischemic inflammatory response, e.g. after myocardial infarction, will be reviewed by Frangioiannis (18). Multiple pathways including oxidative stress, toll-like receptors and complement converge to promote chemokine expression during reperfusion triggering the recruitment of neutrophil and mononuclear cells to the ischemic area. Notably, the functions of chemokines may also extend to the deposition of fibrous tissue and the regulation of angiogenesis, which may contribute to tissue regeneration. Effective repair can be ascribed to a down-regulation of inflammatory chemokines and a recruitment of vascular progenitor cells triggered by CXCL12, which can be transcriptionally up-regulated by inducible factors in response to hypoxia (8). This merits revisiting of hitherto unappreciated non-homeostatic functions of CXCL12 in orchestrating adaptive changes to tissue damage.

The article by Aukrust et al. (19) provides a cautionary note in that a crucial role of chemokines in the pathogenesis of atherosclerotic plaque progression and destabilization with its therapeutic implications cannot be directly extrapolated to a clinical use as biomarkers for cardiovascular risk prediction. Although preliminary studies indicate that some chemokine levels are associated with the risk for future events in acute coronary syndromes, while polymorphisms of chemokine/receptor genes have been linked to atherosclerosis, prognostic applications require verification of their stability and added value in comparison to established diagnostic markers.

A subgroup of chemokines has been found to exert important functions in regulating both physiologic and pathologic angiogenesis, also in the context of chronic inflammation, fibrosis, and malignancy, and even metastasis. On the basis of their structure and receptor binding, individual ligands can display either angiogenic or angiostatic biological activities, which have been summarized by Mehrad et al. (20). Moreover, certain CC chemokines, namely CCL2, can contribute to arteriogenesis required for collateral growth due to effects on macrophage infiltration and endothelial cell migration (21). Interestingly, differential expression of chemokines, in particular an upregulation of CCL2, has also been observed in venous malformations, in conjunction with an arterialization of the endothelium (see article by
Ebenebe et al. in this Theme Issue [22]).

One starts to wonder whether the extensive and comprehensive knowledge that has been gathered on the roles of chemokines and their receptors in many areas of biology and human disease and the availability of the human genome sequence may blunt or at least decelerate further expansion and evolution of this field. However, it is puzzling that beyond the functional interactions and considerable cross-talk between classical chemokines, related groups of chemotactic polypeptides termed ‘chemokine-like function (CLF)’ or ‘micro’-chemokines have emerged. Such peptides, including e.g. defensins, cannot be classified into known chemokine subfamilies but share structural or functional features and can signal through chemokine receptors (23). The evolutionary conserved and ancient cytokine macrophage migration inhibitory factor (MIF) does not only serve pleiotropic functions in various acute and chronic inflammatory diseases, contributing to atherogenesis; it also displays remarkable homology in its tertiary structure with chemokine dimers, namely that of CXCL8. Very recently, the molecular conundrum that underlies the regulation of inflammatory leukocyte migration by MIF has been unravelled. The surprising discovery has been made that MIF is a functional non-cognate ligand for the chemokine receptors CXCR2 and CXCR4, controlling athero-genic and inflammatory leukocyte recruitment (24). In addition, evidence has been provided that targeting MIF as a dual CXCR agonist confers a striking regression and stabilization to manifest atherosclerotic lesions. In a nutshell, these findings epitomize hitherto unappreciated implications for vascular disease and biology that may be imparted by yet to be identified novel molecular and functional interactions among chemokines, their receptors and related peptides.

References