Spotlight on mechanisms of vascular inflammation

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1. Introduction

Understanding the complexity of the inflammatory response is of critical importance in the search for effective therapies for common vascular chronic inflammatory and autoimmune diseases with high morbidity and mortality rates worldwide. This spotlight issue is devoted to reviewing knowledge accumulated over the past few years on the molecular and cellular mechanisms operating in vascular inflammation. Throughout the issue there is also a discussion of current animal models of inflammatory vascular diseases in terms of their similarities and differences in comparison with human conditions.

2. Mechanisms of leucocyte adhesion and extravasation, endothelial cell activation, and inflammation

A general overview of the molecular and cellular actors involved in the inflammatory response is provided by Barreiro et al. The analysis begins at the molecular level, describing the soluble factors and the adhesion and chemotactic receptors that orchestrate the various steps of leucocyte recruitment during inflammation. The cellular structures that are required to mediate the contact between leucocytes and endothelial cells during extravasation are also reviewed. Finally, Barreiro et al. discuss the guidance of different leucocyte subsets (Th1, Th2, Th17, Treg, CD4, CD8, T cell subsets) to specific inflammatory scenarios and the potential of therapeutic strategies based on the blockade of leucocyte guidance.

The theme of guidance is continued by Kubes et al., who discuss the molecular mechanisms underlying leucocyte chemotaxis, comparing in vivo and in vitro models. Immune cells need to migrate in a directed manner to arrive promptly at inflammation sites. During this process, leucocytes establish contacts with and adhere to activated endothelium and then crawl towards a suitable site for extravasation. Integrin-based adhesion is regulated by chemokines via Rap GTPases and their guanine-nucleotide exchange factors such as CalDAG-GEF1; in contrast, intraluminal crawling by leucocytes is governed by β2 integrins and also seems to be Vav-1 dependent. Once leucocytes traverse the endothelium, they have to integrate and prioritize multiple combinatorial chemotactic signals, using for this purpose PI3Kγ/PTEN and SHIP1, among other molecules.

In a related review, Zernecke and Weber provide a thorough compendium of the chemokines and their receptors that play prominent roles in the pathogenesis of atherosclerosis. These authors address, among other issues: the involvement of CCL2 and its receptor CCR2 in early atherosclerotic lesions and in vascular injury; the differential role of CCR1 and CCR5, both receptors for CCL5, at distinct steps of the extravasation process; the recruitment of monocytes and neutrophils induced by CXCR2: the key role of the non-canonical chemokine macrophage migration inhibitory factor (MIF) in atherosclerosis and the regression of established atherosclerotic lesions by blocking MIF antibody treatment; the atheroprotection exerted by the CXCL12/CXCR4 chemotactic axis; the prominent role of the soluble form of CX3CL1 in exacerbating atherosclerosis by promoting monocyte recruitment and survival; the dual role of CXCL16 as scavenger receptor (atheroprotective) and chemotactant (pro-atherogenic): the controversial role of CCL19/CCL21 and their receptor CCR7 in this process; the implication of CXCR3/CXCL10 in the regulation of T-cell responses during atherogenesis; and, finally, the role of the heterodimer CXCL4-CCL5 as an atherosclerosis inducer.

The endothelial signal transduction pathways involved in the transition from leucocyte rolling and firm adhesion to transendothelial migration are described in the review of Hordijk et al. Signals generated upon leucocyte–endothelium interaction or antibody-induced clustering of adhesion receptors cooperate to disassemble interendothelial junctions, enhancing endothelial paracellular permeability and favouring leucocyte transendothelial migration. Central molecules in these pathways are small GTPases (RhoA, RhoG, and Rac1), second messengers [calcium and reactive oxygen species (ROS)], protein kinases (Pyk2 and Src), and phosphatases (PTP1B, VE-PTP and receptor protein tyrosine phosphatase µ). The review also includes an interesting commentary on the effect of diverse pathogens (bacteria, fungi, and viruses) on endothelium. For example, Neisseria meningitidis is able to subvert endothelial cell adhesion molecules and the Par-polarity complex, decreasing leucocyte adhesion and transendothelial migration and increasing paracellular bacterial invasion, and HIV-infected, monocyte-derived macrophages induce the changes in the endothelial protein expression profile that might lead to endothelial permeability dysfunction.

Vascular inflammation is involved in the pathogenesis of hypertension and is a common element in a variety of cardiovascular diseases. In this regard, angiotensin (Ang) II promotes vascular inflammation...
through the activation of transcription factors that induce synthesis of inflammatory mediators. IL-6 is a pleiotropic cytokine secreted in response to pro-inflammatory signals, including Ang II, and has been widely implicated in cardiovascular disease. The review by Brasier,10 presents a clear description of the transcription factor NF-kB as an integrator of the inflammatory process, and differences between ‘canonical’ and ‘non-canonical’ pathways are exposed. The author has paid particular attention to the pathways involved in the activation of NF-kB by Ang II, and the main differences in comparison with TNF-α-activated signalling. The review also discusses signalling involved in monocyte activation and protection from ROS during cellular stress, such as local effects of IL-6 in the vasculature.

Caveolae plasma membrane invaginations are prominent in vascular endothelial cells and a number of other cell types11 and are critically involved in the regulation of vascular tone by regulating eNOS activity. An update of the caveolin and cavin protein families is provided by Chidlow and Sessa.12 Moreover, the involvement and relevance of caveolae and caveolins in disease is discussed in inflammatory conditions, in humans with genetic defects, and in mice deficient for caveolins.13 This first review collecting all the information on cavins will be very useful to the scientific community, since the cell biology and disease implications of this emerging family are likely to overlap significantly with caveolins.

3. Extracellular matrix, inflammation, and the angiogenic response

Angiogenesis and inflammation are often coupled, and many inflammatory stimuli can activate the angiogenic programme of endothelial cells. Matrix remodelling is particularly important during this inflammation-driven angiogenesis. In their review, Arroyo and Iruela-Arispe14 discuss the diverse functions of the extracellular matrix (ECM) in this process, including its remodelling by endothelial cells at the capillary sprout through the action of specific proteases, in particular MT1-MMP. The ECM also provides the tensile forces, adhesion sites, and soluble bioactive agents and growth factors required for vascular morphogenesis. Arroyo and Iruela-Arispe give special emphasis to the need for further ECM remodelling at the inflammatory focus to favour vascular regeneration and proper tissue repair. Angiogenesis is also the theme of the review by Rey and Semenza,15 who discuss the critical role of hypoxia-inducible factor 1 (HIF-1) in the compensatory angiogenic response to insufficient O2 supply. The authors focus on HIF-1 because of its ability to induce numerous angiogenic genes that drive local neangiogenesis (e.g. VEGF), vessel remodelling, arteriogenesis, and the recruitment of circulating angiogenic cells for vasculogenesis (e.g. SDF-1). Work with genetically modified mice supports the key role of HIF-1 in vascular remodelling; moreover, several human cardiac and peripheral conditions linked to vessel dysfunction are associated with HIF-1A single nucleotide polymorphisms and reduced HIF-1 activity. Ischaemic diseases are characterized by insufficient vascularization, whereas angiogenesis in other settings (e.g. in tumour angiogenesis or retinopathy of prematurity) aggravates the disease. The pivotal role of HIF-1 in building the vasculature has stimulated great interest in the potential of pro-HIF-1 or anti-HIF-1 therapies to locally activate or inhibit angiogenesis to treat these diverse conditions.16 This point is discussed in detail in this interesting review, which makes a valuable contribution to bridging the gap between the advances in understanding of the biology of oxygen-sensing pathways and their potential clinical application.

4. Animal models

An update on the potential of 5-lipoxygenase (5-LO) and leucotrienes (LT) as therapeutic targets in cardiovascular disease is given by Poeckel and Funk.17 The review neatly summarizes the role and synthesis of different leucotrienes and their receptors. The authors critically review the effect of targeting this and related pathways in animal models of atherosclerosis, abdominal aortic aneurysm, and myocardial infarction/reperfusion injury. Pre-clinical studies have provided useful information on the effect of targeting the 5-LO/LT pathway, which seems to operate in early atherogenesis rather than in advanced stages. However, mouse studies cannot be directly extrapolated to humans since they differ with respect to the 5-LO/LT pathway. Nonetheless, given the importance of this pathway in inflammatory cardiovascular disease, a challenge for the development of therapeutic interventions in the coming years will be to identify better targets of 5-LO products through the use of cell- and tissue-specific conditionally modified mice.

Excessive cell proliferation is a hallmark of the inflammatory response associated with atherosclerosis, and regulators of cell proliferation therefore deserve special attention as potential therapeutic targets for the treatment of vascular diseases.18 Andres et al.19 summarize the current knowledge on the role of cell-cycle regulators in the development of native and graft atherosclerosis. The authors provide a critical evaluation of recent studies in genetically engineered mice that have analysed the role of specific cell-cycle regulators in atherosclerosis. Moreover, they summarize the mounting evidence from genetic studies in humans that suggests an important role for cell-cycle inhibitors in the protection against coronary artery disease and myocardial infarction.

In summary, this spotlight issue provides valuable updated information on the basic mechanisms operating in the pathogenesis of chronic vascular inflammation and atherosclerosis. Hopefully, this important body of knowledge will be translated into clinical practice in the near future.

Conflict of interest: none declared.

References


