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Mini review

Inflammation in human carotid atheroma plaques

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ABSTRACT

Inflammation in carotid atherosclerotic plaque is linked to plaque rupture and cerebrovascular accidents. The balance between pro- and anti-inflammatory mediators governs development of the plaque, and may mediate enhancement of lesion broadening or, on the contrary, delay progression. In addition to macrophages and endothelial cells, smooth muscle cells (SMCs), which are the dominant cell subset in advanced plaques, are crucial players in carotid atherosclerosis development given their ability to differentiate into distinct phenotypes in reponse to specific signals received from the environment of the lesion. Carotid atheroma SMCs actively contribute to the inflammation in the lesion because of their acquired capacity to produce inflammatory mediators. We review the successive stages of carotid atheroma plaque formation via fatty streak early-stage toward more advanced rupture-prone lesions and document involvement of cytokines and chemokines and their cellular sources and targets in plaque progression and rupture.

1. Introduction

Atherosclerosis is a vascular inflammatory disease that tends to develop at the inner curvatures and branch points of medium and large arteries, such as carotid arteries, that are usually associated with a disturbed blood flow [1]. Carotid atherosclerosis is characterized by thickening of the inner lining of the arterial wall where a plaque is formed composed of infiltrating inflammatory cells such as monocytes, macrophages, T lymphocytes and dendritic cells, in addition to smooth muscle cells (SMCs), extracellular matrix (ECM) proteins, lipids and calcium deposits (Fig. 1) [2]. These plaques can suddenly rupture and produce distal thrombus propagation and hence vessel occlusion resulting in possible ischemic events [1]. Therefore, carotid atherosclerosis is considered a cerebrovascular disease characterized by chronic local inflammation that can promote ischemic stroke events [1].

The management of the inflammatory response in atherosclerosis is carried out by a range of cytokines that act during the distinct stages of the disease regulating both innate and adaptive responses [1]. Here, we review current knowledge on the processes governed by cytokines and chemokines from initial early-stage lesion up to final plaque rupture.

2. Initial stage of carotid atherosclerosis (or early-stage lesion) – fatty streak

The carotid arterial wall consists of three layers, with connective tissue constituting part of the adventitia in the outer layer of the wall, SMCs being found mainly in the media, and endothelial cells (ECs) located in the intima layer in direct contact with the lumen [2]. Thus, the arterial wall is lined by ECs, which are responsible for responding and adapting to changes in the pattern of the blood flow [1]. Shear stress is the stress exerted by the blood parallel to the vessel wall producing frictional force on the endothelial surface and triggering an anti-atherogenic gene expression and signal transduction profile in ECs [3]. Carotid artery wall configuration at bends and bifurcations is associated to and altered by local modifications in blood flow pattern and velocity [4]. These regions of disturbed flow *in vivo* are associated with high rates of both EC proliferation and apoptosis, higher permeability to blood LDL, higher expression of adhesion molecule, inflammatory and chemokine genes, sustained elevation of oxidative stress and increased production of extracellular matrix proteins [2]. Disturbed flow patterns characteristic of atherosclerotic lesions may promote ECs to adopt a pro-inflammatory phenotype expressing molecules including C-C motif chemokine ligand (CCL) 2 and 5, C-X-C motif chemokine ligand (CXCL)

Abbreviations: A, asymptomatic patients (without ischemic event); CEA, carotid endarterectomies; ECs, endothelial cells; oxLDL, oxidized low-density lipoprotein; S, symptomatic patients (suffering ischemic event); SMCs, smooth muscle cells

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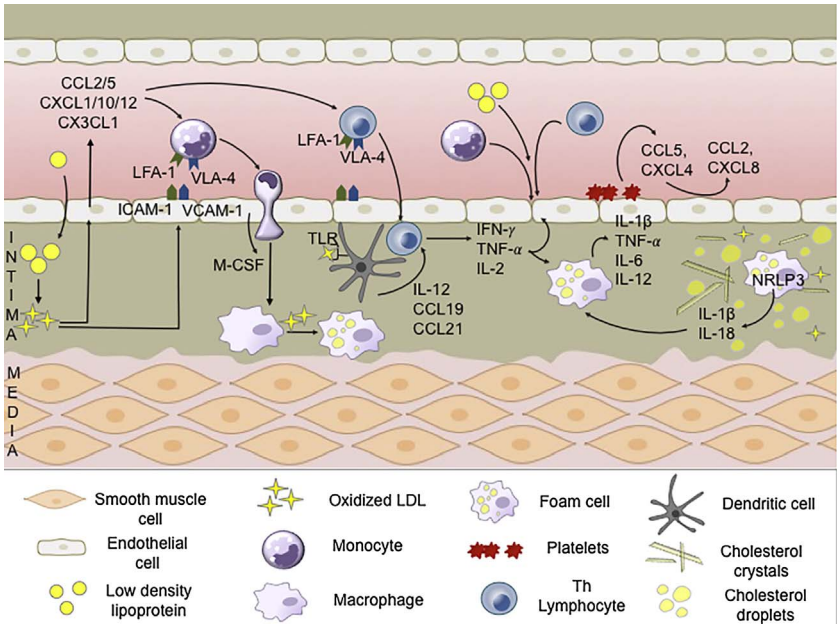

Fig. 1. Initiation of atherosclerotic plaque formation. Following damage to the endothelium LDL molecules enter into the arterial wall and are retained in the intima where they are oxidized (oxLDL). These oxidized particles induce endothelial cells (ECs) to produce adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), and to release the chemokines CCL2, CCL5, CXCL1, CXCL10, CXCL12 and CX3CL1 that attract circulating immune cells from blood. The expression of adhesion molecules VLA-4 and LFA-1 by monocytes and T cells facilitates their entry within the intima. Macrophage colony-stimulating factor (M-CSF) release in the intimal space by oxLDL-stimulated ECs results in differentiation of monocytes into macrophages. The presence of oxLDL molecules promotes macrophages to further differentiate into lipid-loaded foam cells. Resident wall dendritic cells (DCs) are activated through the binding of oxLDL to the membrane Toll-like receptors (TLRs) and hence, release interleukin (IL)-12, CCL19 and CCL21 that drive T cells toward Th1-type-specific differentiation. Platelets are aggregated on the endothelium and release CXCL4 and CCL5 that inhibit EC proliferation and attract monocytes to the lesion site. Additionally, they induce ECs to release CCL2 and CXCL8 to amplifying immune cell attraction to the developing atheroma plaque. IFN-γ, TNF-α and IL-2 produced by Th1 cells activate macrophages to produce pro-inflammatory molecules as well as ECs to produce more adhesion molecules and chemokines. Excessive intra- and extra-cellular cholesterol activates macrophages NRLP3 inflammasome to release IL-1β and IL-18, broadening the inflammatory status of the lesion.

1, 10 and 12, C-X3-C motif chemokine ligand 1 (CX3CL1) [5], macrophage colony-stimulating factor (M-CSF), E/P-selectin [6] and also adhesion molecules such as vascular adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and platelet endothelial cell adhesion molecule-1 (PECAM-1) [1] that attract and recruit blood monocytes, T lymphocytes and dendritic cells (DCs) producing the initial inflammatory response into the intima [7].

Even though chemokines seem to play an important role in immune cell recruitment, particularly monocytes and T cells, the precise interactions and contributions of these immune molecules remain unknown [8]. CCL5 has been studied in some detail [9]. Early events surrounding the initiation of the vascular inflammatory response program to vascular injury are hallmarked by enhanced CCL5 secretion by many cell types, such as ECs, macrophages, vascular SMCs and platelets [10]. Platelets, also attracted to the lesion, were shown to be important contributors to the inflammation by secreting CCL5 after their migration to the endothelial monolayer [10]. Among the multitudinous effects of CCL5, which mainly are pro-inflammatory, T lymphocyte and monocyte chemoattraction are the most characteristic ones [10]. CCL5 has been found to colocalize with both macrophages and T cells within human carotid atheroma plaques [11].

Endothelial cell dysfunction caused by disturbed blood flow allows blood LDL to diffuse passively through EC junctions toward the inside of the injured intima where it is retained [12] by interaction of its apoB100 moiety with ECM components such as proteoglycans [13]. Thus, LDL will be accumulated in the subendothelial space and be exposed to oxidative reactions producing oxidized LDL particles (oxLDL) [2]. The excess of oxLDL is removed from the intima by macrophages that previously have been differentiated from blood monocytes [14]. The macrophage population in early atherosclerotic lesions comes mainly from monocyte differentiation stimulated by M-CSF released by activated endothelial cells [7]. The cytokine milieu within the atherosclerotic plaque can orientate macrophage polarization as Th1 cells promote pro-inflammatory M1 phenotype while Th2 cells are involved in anti-inflammatory M2 phenotype induction [14]. It has been shown also that oxLDL directs human macrophages towards an M1 phenotype yielding a pro-inflammatory state [14]. The continuous presence of oxLDL induces macrophages to up-regulate their scavenger receptors CD36, macrophage scavenger receptor (SR)-A, SR-BI, lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) and CD68, resulting in increased uptake of oxidized LDL particles by themselves [15]. The uptake and accumulation of oxLDL by macrophages is the culprit of their transformation into foam cells [14]. Interestingly, the cytokine milieu within atherosclerotic plaque can govern macrophage polarization and plasticity and hence, facilitate a switch from one phenotype to another [14].

Therefore, high blood LDL levels imply both continued formation of oxLDL particles in the subendothelial space and posterior foam cell accumulation which will form characteristic fatty streaks of initial atherosclerosis. Hence, in this early stage of atherosclerosis, the plaque will consist of several layers of lipid-laden macrophages [2]. Monocyte-derived macrophages will constitute approximately 80% of the leukocytes present in atheroma [6].

Although T cells are recruited in parallel with macrophages by similar mechanisms involving adhesion molecules and chemokines, the ratio of macrophage/T cell in human atherosclerotic lesion is between 4:1 and 10:1 [7]. T cells, mainly of the category of T helper lymphocytes (Th), are supposed to amount to about 5–20% of all leukocytes of the lesion [16]. In carotid atherosclerotic plaques T cells are activated by intimal DCs [17]. DCs in the healthy human artery can be found in close proximity to the endothelium and in the tunica adventitia; however, in atheroma plaques, in addition to these resident DCs, one also finds differentiated DCs derived from blood monocytes [6] attracted by chemotactic factors released by ECs [18]. Activation of DCs in the intima is promoted by their membrane receptors such as Toll-like receptors (TLRs) [19] following interaction with potential danger signals such as released peptide fragments of the main LDL apoprotein, apoB100, present in the plaques [17]. In consequence, these DCs will release naïve T cell-attracting chemokines such as CCL19 and CCL21 [20]. Human arterial studies [20] revealed DC/T cells clusters within the plaques suggesting that a direct activation of T cells by DCs might occur while some DCs may circulate to lymph nodes where they will activate T cells [17]. In the latter case, Th cells are recruited into atherosclerotic plaques, in areas where ECs express adhesion molecules, and they will be re-activated by local DCs through presentation of apoB fragments [17]. This interaction of DC/T cells, in combination with cytokines present in the plaque such as IL-12 released by DCs and monocytes/macrophages, will drive Th cells toward Th1-type-specific differentiation with [21] expression of IFN-γ, TNF-α and IL-2 [22].

IFN-γ and TNF-α may enhance permeability via reorganization of the cytoskeleton in ECs, opening up gaps between adjacent cells [23] and furthermore, IFN-γ potentiates VCAM-1 expression in endothelial cells [6]. Therefore, the activation of the endothelium increases the permeability to LDL macromolecules and immune cells, and hence, aggravates the progress of the injury [3].

IFN-γ also mediates the up-regulation of oxLDL scavenger receptors