CXCL4 in atherosclerosis: Possible roles in monocyte arrest and macrophage foam cell formation

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In this issue of Thrombosis and Haemostasis, Sachais et al. demonstrate a critical role for platelet factor 4 (CXCL4) in the development of atherosclerosis (1). In two mouse models, CXCL4 deficiency induced by gene targeting and homologous recombination resulted in reduction of atherosclerotic lesion size without affecting platelet activation or changing cholesterol levels. CXCL4 was one of the first chemokines to be discovered (2), but its role has remained largely enigmatic. The presence of platelets in atherosclerotic lesions is well documented (3). Based on mouse models, a role of platelet-derived chemokines for monocyte recruitment to the arterial wall has been postulated previously (4, 5). CXCL4 is also found in atherosclerotic lesions of human carotid arteries (6), suggesting a role in atherogenesis.

CXCL4 has a number of biological effects, which depend on the target cell type. CXCL4 can induce chemokine or cytokine release and inhibit or promote cell differentiation (7). At least two of these effects are likely to be important during the development of atherosclerotic plaque (Fig.1).

CXCL4 has been shown to play a role in monocyte recruitment to the arterial wall. Monocytes are recruited to atherosclerotic lesions in a cascade-like fashion (8), and platelets promote their arrest and recruitment (3–5). CXCL4 interacts with another chemokine, CCL5, also known as RANTES (regulated on activation normal T-cell expressed and secreted). Whereas CXCL4 alone does not affect monocyte arrest on activated endothelial cells under flow, the combination of CXCL4 with CCL5 results in an effect greater than CCL5 alone (9). Three possible explanations have been discussed for this finding: CXCL4 may form heterodimers with CCL5 and thereby increase CCL5 binding to monocytes by supplying additional binding sites, or dimerization of CXCL4 with CCL5 may induce heterodimerization of chemokine receptors, which might modulate intracellular signaling. Alternatively, CXCL4 signaling might enhance CCL5-dependent effects, e.g. by a common pathway involving p38 mitogen-activated kinase in monocytes (9). The exact mechanisms, however, have still to be elucidated.

CXCL4 may also increase atherogenesis by promoting differentiation of monocytes into macrophages and foam cells (10). Consistent with this, Sachais et al. demonstrate localization of CXCL4 in murine atherosclerotic plaque close to foam cells. It is known that macrophages differentiated from monocytes under the influence of CXCL4 are in some respect different from those differentiated in the presence of M-CSF (11). M-CSF has been clearly demonstrated to play a crucial role in atherogenesis as demonstrated in M-CSF deficient op/op mice (12). During mac-

Figure 1: Possible roles of CXCL4 in atherosclerosis. CXCL4 (Δ) together with CCL5 (▲) can be immobilized on the endothelial surface and promote monocyte arrest. Interstitial CXCL4 may promote macrophage formation from monocytes (bold arrow) that can further differentiate to foam cells (thin arrow).

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rophage differentiation, CXCL4 induces phagocytosis and generation of reactive oxygen species (13). Furthermore, macrophages differentiated under the influence of CXCL4 lack surface expression of HLA-DR and do not promote T-cell proliferation, suggesting polarization to a macrophage phenotype (7). Presence of CXCL4 reduces binding of native low-density lipoprotein (LDL) — another key player in atherosogenesis — to its receptor, thereby potentially promoting LDL oxidation (14). On the other hand, CXCL4 bound to oxidized LDL increases its binding to macrophages and enhances esterification of oxidized LDL in macrophages (15). We have recently investigated gene expression during foam cell formation induced by treating macrophages differentiated from human monocytes with either M-CSF or CXCL4 with oxidized LDL (11). Overall, gene regulation in cells differentiated with CXCL4 was similar to that of those differentiated with M-CSF. Interestingly, the CXCL4 foam cells responded to exposure to oxLDL with regulation of more genes than those differentiated with M-CSF. Like M-CSF-induced foam cells, CXCL4-induced foam cells displayed a gene regulation pattern similar to that of dendritic cells (11).

Apart from the mechanisms suggested above, CXCL4 may affect other cells involved in atherogenesis like endothelial cells or T cells. It is still unclear which receptors are involved in CXCL4 effects on monocyte arrest and differentiation. One candidate receptor is CXCR3B, a CXCR3 splice variant, which has been described to bind CXCL4 and induce downstream signaling (16). Other “receptors” for CXCL4 are cell surface glycosaminoglycans (17). Clinically, anti-platelet therapies are commonly used in atherosclerosis patients. It is unclear what influence such therapies might have on CXCL4 secretion. Finally, it remains to be determined whether specific blockade of CXCL4 effects represents a suitable approach to prevent the development and progression of atherosclerotic lesions. The paper by Sachais et al. suggests that this possibility should be explored.

References