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Editorial comment

Chemokines: the link between inflammation, restenosis and atherosclerosis?[☆]

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Atherosclerosis is an inflammatory disease [1]. Key evidence of this is the initial influx of monocytes and T-lymphocytes into the vessel wall in response to injury to the endothelium. Mediators of this migration are probably crucial in plaque development, but remain largely undefined. Potential offenders include, however, chemokines — a superfamily group of chemotactic cytokines. In this issue, Economou et al. highlight the potential atherogenic role of one of these substances — monocyte chemoattractant protein 1 (MCP-1).

So what exactly are chemokines? Well, they comprise small molecules (8–10-kD) and can be divided into at least four families, according to the arrangement of their cysteine residues. The α - and β -chemokines contain four cysteines and appear to be the largest two families. In α -chemokines the first two cysteines are separated by a single amino acid (CXC chemokines), while in β -chemokines the first two cysteines are directly connected to one another (CC chemokines). Representatives of the other two families include fractalkine, (which has three amino acids between its cysteine residues [CX₃C]), and lymphotactin, which contains only one cysteine residue [2].

Considerable evidence already implicates MCP-1

in atherogenesis. For example, MCP-1 expression of the chemokine detected in endothelial cells, macrophages and smooth muscle cells (SMCs) of human atherosclerotic plaques [3]. Also, artificially-induced hypercholesterolaemia in primates prompts carotid SMCs to express MCP-1 [4]. This finding has 'fuelled' speculation that the sustained expression of MCP-1 might both trigger the initial influx of macrophages into the vessel wall and help to perpetuate atherosclerosis [5]. Equally intriguing are studies showing that mice lacking either MCP-1 or its receptor (CCR2) are unusually resistant to the development of atherosclerotic lesions [6,7].

Economou et al. have now widened these arguments by demonstrating that patients have raised serum MCP-1 levels by 3 and 6 months following percutaneous transluminal coronary angioplasty (PTCA). Their work supports data from porcine models, in which vessels subjected to balloon-mediated injury show heightened expression of MCP-1 [8].

Evidence does point to suggest that increased MCP-1 expression following PTCA might contribute coronary restenosis — and that this is not just guesswork. Hokimoto et al. [9] have reported an association between raised plasma levels of MCP-1 and restenosis 3 months after coronary intervention. However, whether MCP-1 is a marker or a mediator of restenosis is not known. It is still not clear whether the chemokine originates from injured SMCs (and so trigger atherogenesis) or from infiltrating monocyte/macrophages (i.e. after atherogenesis has begun).

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Animal studies have provided conflicting data on whether MCP-1 alters regulation of vascular SMCs, the predominant cell type in restenosis [10,11]. More promising, though, is evidence that adenovirus-induced expression of MCP-1 can lead to a functional switch in smooth muscle from the contractile to the synthetic phenotype found in atheroma [12]. Economou et al. also report significant increase in basal MCP-1 levels in patients with coronary atheroma compared with 'normal' controls. By contrast, Inadera et al. found no such difference between patients with atherosclerosis and disease-free people [13]. This discrepancy could be because Economou et al. did not control MCP-1 levels for age, gender and plasma triglyceride concentrations. These known confounding variables may account for the moderate discrepancy in baseline levels of MCP-1 in patients studied by Economou et al. and those in the investigation by Hokimoto et al.

It is possible, of course, that other chemokines play a role in atherosclerosis. Take eotaxin. This, like MCP-1, is a β -chemokine and its plasma levels appear raised in patients with coronary atherosclerosis. At first glance, this seems odd given that eotaxin was initially described as a chemotactic factor for eosinophils, cells are rarely found in atherosclerotic lesions. Even so, there is some evidence implicating eotaxin in atherosclerosis. A recent in-vitro study has shown that vascular SMCs can express eotaxin RNA in response to tumour necrosis factor- α . Subsequent immunohistochemistry studies have localised eotaxin to vascular SMCs and the chemokine's receptor (CCR3), to macrophages, within human atherosclerotic plaques [14]. Mounting evidence suggests that eotaxin regulates cells other than eosinophils and so might help mediate vascular inflammation. An obvious challenge now is to determine whether there is any relation between eotaxin levels and the extent and severity of coronary atheroma, and also whether 'manipulation' of this chemokine affects plaque formation and progression.

We remain hazy about whether and how chemokines are involved in atherosclerosis, plaque rupture and post-angioplasty restenosis. Unravelling the functions and interactions of these molecules can only increase our understanding of the pathogenesis of coronary vascular disease and may indicate new therapeutic strategies.

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