Chemokines and their receptors: potential therapeutic targets?

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Chemokines and their receptors are crucial mediators and regulators of leukocyte trafficking and homeostasis during immune surveillance and inflammation, which underlie the development and progression of atherosclerosis. The abundance of chemokines suggests that specific functional roles, with cooperative or synergistic interactions between the chemokine subfamilies provide a balance between proinflammatory and anti-inflammatory activities. The challenge for researchers has been identifying relevant interactions that may favour atheroprotection. ‘Increased understanding of these processes has highlighted possible targetable mechanisms.’

Chemokines or chemokine receptors shown to play a role in atherosclerosis include CXCR3 and its ligands, which are active on effector T cells, CCR2 and CX3CR1 and their respective ligands CCL2 and CX3CL1, which attract monocytes, and CCR5 with its ligand CCL5, which is involved in the recruitment of both T cells and monocytes. However, new insights have implicated novel chemokines, as well as novel targets for their actions, in atherogenesis.

Studies have shown a link between dendritic cells and Tregulatory (Treg) cells in atherosclerosis, controlled via chemokine CCL17. In hyperlipidemic mice, deficiency of CCL17 reduced atherosclerotic lesion formation, and this was associated with a decrease in the number of macrophages and CD3\(^+\) T cells in the plaques. In contrast, CCL17 was involved in the recruitment of CD4\(^+\) T cells to sites of inflammation. Accumulation of Treg in the lymph nodes and aortas of CCL17 deficient mice was explained by the control of Treg homeostasis through a CCL17-expressing dendritic cell subset in the lesions of hyperlipidemic mice. Co-incubation of CD4\(^+\) T cells with CCL17 deficient dendritic cells enhanced expansion of Treg and was also accompanied by lower numbers of apoptotic Treg, implying that CCL17 mediates suppression of Treg proliferation. These data therefore implicate the dendritic cell-derived CCL17 as a central regulator of Tregulatory cell homeostasis, and suggest that CCL17 may be a potential target for vascular therapy.

Other studies have identified chemokine effects on other blood cell types involved in vascular inflammation, in particular neutrophils and platelets. Increased circulating neutrophil counts have been shown to accelerate atherosclerosis, particularly in early stages. Studies have shown that CXCL1–CXCR2 and CCR1, -2 and -5 were responsible for the mobilisation and infiltration of
neutrophils into sites of arterial inflammation, implying a role in promotion of atherosclerosis by mediating the trafficking of inflammatory neutrophils to newly developing plaques.

Increased understanding of the involvement of chemokines in inflammation and immunity in turn suggests the possibility of targeted therapeutic intervention. For example, inhibition of CXCR2, thereby inhibiting the influx of neutrophils, may offer potential benefit in the prevention of atherosclerosis in high-risk patients.

Alternative therapeutic approaches include structural modification of chemokines resulting in potent antagonists. The prototype for this approach is an N-methionylated variant of CCL5 (Met-RANTES). Administration of Met-RANTES has been shown to exert beneficial effects in various mouse models of inflammatory disease, including atherosclerosis and neointima formation after arterial injury. Another possibility involves disruption of pro-atherogenic heteromeric complexes of the platelet-derived chemokines CCL5 and CXCL4. The resultant synthetic peptide MKEY was shown to significantly reduce atherosclerotic lesion formation in hyperlipidemic mice, due to a reduction of lesional macrophage accumulation. Activity of this peptide required both CCL5 and CXCL4, indicating specificity of antagonism with normal immune functions unaffected by disruption of CCL5–CXCL4 heteromerisation.

Finally, atheroprotective chemokine interactions may offer therapeutic potential. Previous studies have shown that transfer of microRNA-126 (miR-126) from apoptotic bodies in endothelial cells to neighbouring vascular cells elicited CXCL12-mediated vasoprotection. The ubiquitous distribution of CXCL12 highlights the need for regional application of targeting strategies.

‘Targeting the chemokine system offers novel strategies for potential therapeutic benefit in preventing or treating inflammatory disorders, such as atherosclerosis,’ concluded Professor Weber.

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