A Functional Role for Eotaxin-2 in the Initiation and Progression of Experimental Atheroma

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The chemokine eotaxin-2 is a potent chemoattractant for inflammatory cells, the predominant of which are eosinophils. Eotaxin-2 binds to the eosinophil receptor CCL24, also named CCR3, and possesses a potent chemotactic activity for eosinophils. Human and murine atherosclerotic plaques are known to exhibit inflammatory phenotypes where a complex interaction of cytokined and chemokines play a role. We tested the hypothesis that eotaxin-2 plays a causative role in the initiation and progression of atherosclerosis.

Employing reverse-transcriptase PCR analysis, we have shown that eotaxin-2 is abundantly expressed in plaque from apoE knockout (KO) mice. Administration of polyclonal blocking antibodies to eotaxin-2 resulted in a robust reduction of early atherosclerotic plaques in apoE KO mice whereas prolonged treatment of mice with advanced plaques led to atheroma stabilization. A neutralizing monoclonal antibody (1D8) against eotaxin-2, produced in our laboratory, significantly attenuated adhesion of lymphocytes and monocytes as well as heart-derived H5V cells to fibronectin and successfully inhibited their migration towards VEGF. Furthermore, we have shown that 1D8 interferes with binding of eotaxin-2 to the chemokine-recognition site on CCR3. Similar to the polyclonal antibodies, 1D8 significantly reduced atherosclerotic plaques in apoE KO mice, pointing out to the promising therapeutic potential of this monoclonal antibody.

Conclusion. Eotaxin-2 represents a novel target in human atheroma and its blockade by neutralizing antibodies is associated with reduced fatty streak accumulation and plaque stabilization in mice.