

# Vascular CXCR4 Limits Atherosclerosis by Maintaining Arterial Integrity

## Evidence From Mouse and Human Studies

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The CXCL12/CXCR4 chemokine ligand/receptor axis controls (progenitor) cell homeostasis and trafficking. So far, an atheroprotective role of CXCL12/CXCR4 has only been implied through pharmacological intervention, in particular, because the somatic deletion of the *CXCR4* gene in mice is embryonically lethal. Moreover, cell-specific effects of CXCR4 in the arterial wall and underlying mechanisms remain elusive, prompting us to investigate the relevance of CXCR4 in vascular cell types for atheroprotection.

Thus, we examined the role of vascular CXCR4 in atherosclerosis by inducing an endothelial cell (BmxCreERT2-driven)-specific or smooth muscle cell (SMC, SmmhcCreERT2- or TaglnCre-driven)-specific deficiency of *CXCR4* in an apolipoprotein E-deficient mouse model.

The cell-specific deletion of *CXCR4* in arterial endothelial cells or smooth muscle cells markedly increased atherosclerotic lesion formation in hyperlipidemic mice. Endothelial barrier function was promoted by CXCL12/CXCR4, which triggered Akt/WNT/ $\beta$ -catenin signaling to drive VE-cadherin expression and stabilized junctional VE-cadherin complexes through associated phosphatases. Conversely, endothelial *CXCR4* deficiency caused arterial leakage and inflammatory leukocyte recruitment during atherogenesis. In arterial smooth muscle cells, CXCR4 sustained normal vascular reactivity and contractile responses, whereas *CXCR4* deficiency favored a synthetic smooth muscle cell phenotype, the occurrence of macrophage-like smooth muscle cells in the lesions, and impaired cholesterol efflux. Furthermore, regression analyses in humans identified the C-allele at *rs2322864* within the *CXCR4* locus to be associated with increased risk for coronary heart disease. In line, C/C risk genotype carriers showed reduced CXCR4 expression in carotid artery plaques, which was furthermore associated with symptomatic disease.

In conclusion, our data clearly establish that vascular CXCR4 limits atherosclerosis by maintaining i) arterial integrity, preserving endothelial barrier function, and ii) a normal contractile smooth muscle cell phenotype. Enhancing these beneficial functions of arterial CXCR4 by selective modulators might open novel therapeutic options in atherosclerosis.