In this issue of *Circulation Research*, Lingrel and colleagues describe the phenotype of myeloid-specific Klf2 knockout mice. Although this transcription factor has long been known to be involved in protection from atherosclerosis, the cell type responsible was not clear.

**Article, see p 1294**

Chronic inflammatory diseases, such as atherosclerosis, are associated with imbalanced recruitment of monocytes and neutrophils to the impaired tissue. Neutrophils are among the first cells detected in developing atherosclerotic plaque. As early as in fatty streaks, monocytes enter the nascent lesions and can differentiate into macrophages. Lineage and microenvironmental stimuli determine the macrophages’ phenotypic and biological functions, with proinflammatory classically activated (M1) and tissue remodeling alternatively activated (M2) as the 2 extremes. Both M1 and M2 macrophages have been shown to be present in atherosclerotic lesions. M1 macrophages were shown to localize in lipid-rich zones whereas M2 macrophages reside in low lipid areas with high cellularity.

Krüppel-like factor (Klf)-2 belongs to the zinc finger family of DNA-binding transcription factors. Klf family members are homologs to the *Drosophila* protein Krüppel. *Drosophila* Krüppel embryonic (homozygous knockout) have defective anterior abdominal and thoracic segments causing lethality. There have been 17 mammalian KLFs identified (Klf1 to Klf17). KLFs have been recognized as playing key roles in controlling cellular processes in many different cell types; however, the best-established role is KLF2 in endothelial cells. Klf2 was shown to be a potent inhibitor of cytokine-mediated induction of VCAM-1 and E-selectin expression in endothelial cells. Interestingly, several studies suggest a link between KLF2 and statins in atherosclerosis. Statins have been reported to induce expression of endothelial NO synthase and thrombomodulin in a KLF2 dependent manner. Statins were shown to induce KLF2 expression in endothelial cells as well as T cells. In mice, Klf2 deficiency is lethal, because it is required for normal tunica media formation and blood vessel stabilization during murine embryogenesis. Hemizygous deficiency of Klf2 intensifies atherosclerosis in hypercholesterolemic mice.

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Lingrel et al describe a 22% increase in aortic root lesion size in myeloid-specific Klf2 knockout mice on the *Ldlr*−/− background (a standard model of atherosclerosis), with no change in blood lipids. Although monocyte polarization to M1 (IL-6, NOS2) and M2 (Fizz1) was slightly reduced, the authors attribute enhanced atherosclerosis to increased adhesion of peritoneal macrophages and neutrophils to an endothelial cell line. Such static adhesion assays do not predict recruitment under flow conditions, but increased numbers of macrophages and neutrophils in atherosclerotic lesions of the aortic root suggest that myeloid-specific ablation of Klf2 might enhance recruitment of these cells, associated with increased detection of myeloperoxidase, chlorotyrosine, and nitrotyrosine in the tissue. Other mechanisms could include reduced egress or reduced apoptosis of myeloid cells. Because neutrophil viability in Klf2-deficient is actually slightly reduced, the latter seem less likely.

The present report does not identify the mechanism by which absence of Klf2 in myeloid cells enhances atherosclerosis, but it describes an important new tool, the myeloid-specific Klf2 knockout mouse. This mouse will be instrumental for future work in the atherosclerosis field.

**Disclosures**

None.

**References**


Protective Role for Myeloid Specific KLF2 in Atherosclerosis
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