Selective Depletion of Macrophages in Atherosclerotic Plaques
Myth, Hype, or Reality?

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In recent years, various animal models showed that macrophages are ubiquitous in all stages of atherosclerosis, and that they have a tremendous impact on lesion progression. The osteopetrotic (op) mouse, for example, has a spontaneously derived mutation in the gene encoding macrophage colony-stimulating factor, resulting in severely reduced blood monocytes and peritoneal macrophages. In an apolipoprotein E-deficient background, these mice reveal significantly less atherosclerosis in the proximal aorta. Macrophages initially exert their principal influence by acting as scavenger cells because of their capacity to phagocytose and remove noxious substances such as modified LDL. Ultimately, their role may shift so that they can act as a source of potent growth-regulatory molecules, cytokines, growth factors, and proteases that facilitate the remodeling of the extracellular matrix and encourage the recruitment of smooth muscle cells (SMCs) (Figure 1). Although these events have been well described by several groups, the role of macrophages in advanced plaques is less clear. First of all, macrophages are involved in atherosclerotic plaque destabilization, as plaques tend to rupture at sites of increased macrophage content. Plaque destabilization is triggered by macrophages through the induction of SMC death and the release of matrix metalloproteinases, which in turn results in reduced synthesis of collagen and thinning of the fibrous cap, respectively (Figure 1). However, in addition to promoting cell death, macrophages in advanced plaques also undergo apoptosis. The majority of apoptotic macrophages surrounds the necrotic core, where they promote core development, and localizes to sites of plaque rupture, suggesting that macrophage death itself promotes plaque instability.

In this issue of Circulation Research, Stoneman et al propose a novel transgenic mouse model to study more in depth the role of monocyte/macrophages both in atherogenesis and established plaques. This mouse strain expresses the human diphtheria toxin receptor (hDTR) from a monocyte/macrophage-specific CD11b promoter sequence so that conditional ablation of monocyte/macrophages can be achieved by intraperitoneal injection of diphtheria toxin (DT). Using this model, Stoneman et al confirm that macrophages play an important role during atherogenesis. They show that DT treatment markedly reduced plaque development in CD11b-DTR mice, most likely by monocyte killing in the circulation with subsequent reduced migration and by inducing macrophage apoptosis in the developing plaque (Figure 2). Furthermore, they demonstrate that DT inhibits lipid uptake of viable macrophages in vitro. However, despite selective induction of macrophage death, the relative proportions of macrophages and SMCs in the plaques of these mice remained unchanged. This finding suggests that SMC accumulation is regulated by growth factors derived from macrophages. Also SMC function may depend on macrophages, as DT reduced collagen content of the plaques.

The CD11b-DTR mouse model that was developed by Stoneman et al is particularly interesting because the role of monocytes/macrophages can also be examined in established plaques. Stoneman et al found that acute (72 hours) DT treatment of plaques in CD11b-DTR mice at 22 weeks of age induced extensive macrophage apoptosis and reduced macrophage content (Figure 2), but did not induce plaque inflammation, thrombosis or rupture. In view of this finding, macrophage death does not directly contribute to plaque destabilization. On the contrary, the study by Stoneman et al clearly suggests that macrophages can be cleared from atherosclerotic plaques in a clean and safe way via selective induction of macrophage apoptosis. However, recent evidence suggests that a number of factors in advanced lesions may contribute to defective phagocytic clearance of apoptotic macrophages, leading to secondary necrosis of these cells and a proinflammatory response. In early lesions, where phagocytic clearance of apoptotic cells appears to be efficient, macrophage apoptosis is associated with diminished lesion cellularity and decreased lesion progression. Thus, the ability, or lack thereof, of lesion macrophages to safely clear apoptotic macrophages seems to be an important determinant of acute atherothrombotic events. Because plaques in CD11b-DTR mice at 22 weeks of age show advanced features, it is plausible that the inflammatory response after induction of macrophage apoptosis is suppressed because of reduced levels of circulating monocytes in these mice and the lethal action of DT on monocytes that succeed to infiltrate the plaque.

Because selective induction of macrophage death may be a promising approach to stabilize “vulnerable”, rupture-prone lesions, this method now gains increasing attention in cardiovascular medicine. Several successful strategies have recently been reported to induce macrophage cell death in atheroscle-
The role of macrophages (MΦ) in atherogenesis and plaque destabilization. Macrophages appear to be the principal cellular mediator of atherogenesis. In advanced plaques, macrophages contribute to plaque destabilization by synthesizing matrix metalloproteinases (MMPs) and by inducing SMC apoptosis. Macrophages also undergo apoptosis and necrotic death, thereby promoting necrotic core formation.

In conclusion, the study by Stoneman et al.13 provides important insights into the role of macrophages in atherogenesis and plaque stability. Because DT-induced macrophage death does not induce inflammation or markers of plaque rupture, their findings justify therapeutic means to selectively remove macrophages to prevent acute coronary syndromes and sudden death. However, combined therapy with statins or other compounds may be needed for a long-term macrophage depleitory effect in atherosclerotic plaques.

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Disclosures
None.

References


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