Editorial

Bone Marrow–Derived Matrix Metalloproteinase-14
A Novel Target for Plaque Stability

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Our understanding of the role of bone marrow (BM)–derived cells in the pathogenesis of vascular disease has been evolving rapidly. It is generally accepted that circulating monocytes, the precursors of macrophages, migrate to the vascular wall and differentiate into lipid-laden macrophages in the process of atherogenesis.[1] BM-derived cells with smooth muscle cell (SMC)–like phenotype also participate in the pathogenesis of vascular disease.[2,3] Circulating endothelial progenitor cells migrate to the site of vascular injury and participate in arterial repair and angiogenesis.[4] A recent study revealed an important role of T cells in hypertension and vascular dysfunction.[5] The vasculature possesses several agonist/receptor systems that affect recruitment and differentiation of BM-derived cells, including granulocyte-macrophage colony stimulating factor,[6] stromal cell–derived factor-1,[7] and erythropoietin.[8,9] These accumulating findings have established the role of BM-derived cells (eg, macrophages, lymphocytes, and vascular progenitors) in the pathogenesis of cardiovascular disease. Activated SMCs, macrophages, and immune cells are abundant in vulnerable atheroma that is often covered with a thin and collagen-poor fibrous cap and/or aggregating platelets (the Figure). Activated SMCs and macrophages are major cell components that produce matrix metalloproteinases (MMPs) in the atherosclerosis plaque. MMPs degrade extracellular matrix and play crucial roles in the pathogenesis of plaque disruption and subsequent thrombosis.[10] Among these MMPs, MMP-14 is a membrane-bound MMP that activates pro–MMP-2 and is closely associated with migration of monocyte-derived cells.[11] However, the role of MMP-14 in atherosclerosis in vivo remains poorly defined.

Article p 931

In the current issue of *Circulation*, Schneider et al[12] examined whether genetic deletion of MMP-14 in BM-derived cells affects atherosclerosis development and plaque stability. In this study, cholesterol-fed low-density lipoprotein receptor–deficient ($Ldlr^{-/-}$) mice were lethally irradiated and reconstituted with BM cells of $Mmp14^{-/-}$ or $Mmp14^{+/+}$ mice. Surprisingly, $Ldlr^{-/-}$ mice engrafted with $Mmp14^{-/-}$ BM did not show any difference in plaque size or macrophage/SMC content in atherosclerotic lesions compared with those with $Mmp14^{+/+}$ BM.[12] In contrast, the plaques in $Ldlr^{-/-}$ mice engrafted with $Mmp14^{-/-}$ BM contained significantly more interstitial collagen than those with $Mmp14^{+/+}$ BM. Finally, BM-derived macrophages from $Mmp14^{-/-}$ mice had significantly less interstitial collagenase activity than those from $Mmp14^{+/+}$ mice in vitro.

The Schneider et al[12] study is important in that it is the first to show the significant role of MMP-14 in plaque vulnerability in vivo. Their finding that the collagen content of atherosclerotic plaque was increased in chimeric mice with $Mmp14^{-/-}$ BM was explained by altered macrophage function in atherosclerotic plaque. It has been shown that MMP-14 is expressed in SMCs and macrophages in human coronary arteries.[13] Monocyte-derived macrophages appear to be one of the major cell components that are incorporated into atherosclerotic plaque (the Figure). It has been demonstrated that BM-derived SMCs are localized to the surface of atherosclerotic plaque in mice[3] and in patients with sex-mismatched BM transplantation.[14] Additionally, a recent study demonstrated that circulating SMC progenitors play an important role in plaque stability by increasing collagen and SMC content in atherosclerotic plaque.[15] However, Schneider et al observed no difference in plaque size or SMC/macrophage content in atherosclerotic lesions between the chimeric mice with $Mmp14^{-/-}$ BM and those with $Mmp\ 14^{+/+}$ BM.[12] These results indicate that plaque stability mediated by BM-derived SMCs is not strongly affected by their MMP-14 deficiency. Thus, other mechanisms for the effects of MMP-14 deficiency in BM-derived cells should be considered. BM-derived platelets also contain and release several MMPs, including MMP-2 and MMP-14, which regulate platelet adhesion and platelet-leukocyte aggregation. All kinds of MMP-$14^{-/-}$ immune cells, including mast cells and regulatory T cells, could contribute to the immune status that enhances plaque stability (the Figure).[16] Indeed, in addition to the BM-derived immune cells, abundant tissue-resident progenitors in the vascular wall also can differentiate into SMCs in transplant atherosclerotic lesions.[17] Furthermore, it has been demonstrated that healing SMCs are derived entirely from the local artery in apolipoprotein E–deficient mice,[18] supporting the long-standing notion that plaque healing is mediated by local proliferating SMCs. It is noteworthy that Schneider et al observed that MMP-14^{+} cells clearly covered the plaque surface in the chimeric mice with $Mmp14^{-/-}$ BM, suggesting that the MMP-14^{+} recipient–derived cells migrated and covered the plaque composed of MMP-14^{-} BM-derived cells (the Figure).[12] Taken together, the interac-

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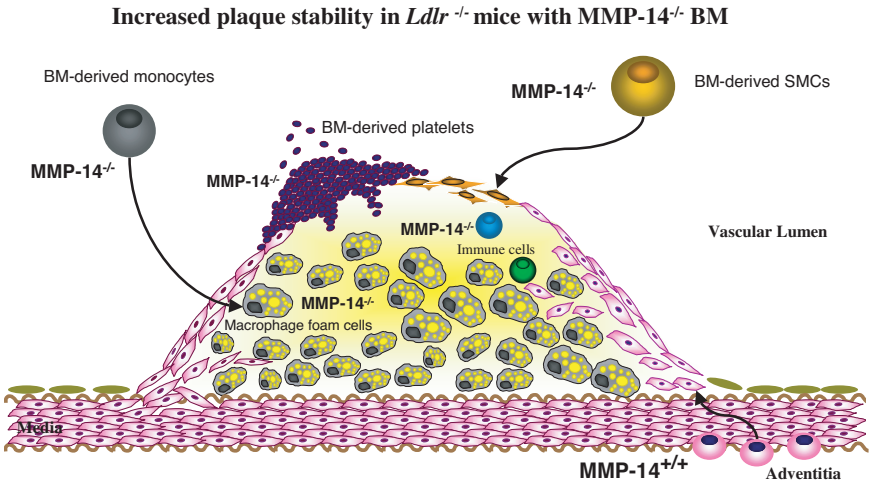

Figure. Role of MMP-14 in BM-derived cells in the pathogenesis of plaque vulnerability. BM-derived cells are the important cell components in advanced atherosclerotic lesions. In this issue, Schneider et al[12] showed that MMP-14 deficiency increases collagen content in plaque composition and promotes changes toward a stable phenotype in mice.

tion between BM-derived cells and recipient-derived cells in the plaque may be an important factor for plaque stability. At present, no plausible explanation exists for the discrepancy between plaque stability and plaque size and SMC/macrophage content in the chimeric mice with *Mmp14*$^{-/-}$ BM. Several important issues remain to be addressed in future studies, including the development of conditional knockout mice that clearly define the role of MMP-14 in each cell component and their function, an identification of effective pharmacological therapies that modulate MMP-14, and an elucidation of possible alterations in endothelial progenitor cells.

What are the clinical implications of this study? Schneider et al[12] suggested that MMP-14 in BM-derived cells could be a causal factor for plaque vulnerability. In contrast, impaired angiogenesis also has been observed in *Mmp14*$^{-/-}$ mice.[19] Therefore, MMP-14 could be an important mediator for angiogenesis through extracellular matrix degradation. These findings suggest that MMP-14 plays an important role in the pathogenesis of plaque vulnerability, whereas it also plays a beneficial role in the mechanism of angiogenesis in ischemic tissue. It has been suggested that statins exert dose-dependent biphasic effects on angiogenesis; they enhance and inhibit angiogenesis at low and high doses, respectively.[20] The dual roles of statins are complex and varied, depending on organs, cell types, and disease stages.[20] The complex effects of MMPs and statins indicate that future studies are needed to confirm the safety level of lipid-lowering therapy that is effective in atherosclerotic patients with ischemic cardiovascular diseases.

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Disclosures

None.

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