Editorial

ADAM17

A Molecular Switch to Control TNFR2 During Atherogenesis In Vivo

Yiting Jia, Wei Kong

A disintegrin and metalloproteinase 17 (ADAM17) is a major sheddase of membrane-anchored cytokines, cell adhesion molecules, receptors, ligands, and enzymes, such as tumor necrosis factor-α (TNF-α), transforming growth factor-α, TNF-α receptor 1 (TNFR1), TNF-α receptor 2 (TNFR2), and interleukin-6 receptor, L-selectin, Notch, and angiotensin-converting enzyme type 2, in which way ADAM17 could modulate a variety of signaling transduction and affect cell behavior.[1–4] The consequence of shedding events mainly depends on the type of substrate shed, the generation of soluble receptor agonists or antagonists, and the cell type and specific tissues affected during various disease states.

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ADAM17 was first identified to process membrane-bound TNF-α precursor to a soluble form. In addition, TNF receptors, TNFR1 and TNFR2, are both ADAM17 substrates. The potent cytokine TNF-α and TNF receptor signaling pathways control cell apoptosis, proliferation, adhesion, and inflammation and thus play an important role in pathogenesis and progression of several cardiovascular processes, including atherosclerosis.[5,6] TNFR1 is proved to be associated with aging-related coronary artery disease in humans, whereas TNFR2-deficient mice exhibit decreased plaque formation.[7,8] Interestingly, ADAM17 has been described to be upregulated in human and mouse atherosclerotic plaques,[7,8] and increased level of ADAM17 may contribute to atherosclerosis resistance,[9,10] which indicated a correlation between ADAM17, TNF signaling, and arteriosclerosis. Unfortunately, ADAM17 knockout mice are not viable because of its essential role in normal fetal development.[11] Mice with targeted deletion of exon 11 that encodes the catalytic active site of the metalloprotease domain (ADAM17$^{\Delta Zn/\Delta Zn}$) also showed perinatal lethality within 2 weeks.[12] Then the conditional ADAM17 knockout animals have been generated to study the role of ADAM17 in physiological bone remodeling and neurological diseases.[13] However, the function of ADAM17 deficiency in atherosclerosis is still in the mist. Recently, Chalaris et al generated partial deletion Adam 17$^{ex/ex}$ mice that showed only a weak ADAM17 expression in tissues, which may point the way to study the role of ADAM17 deficiency in atherosclerosis.[14]

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Nicolaou et al[15] crossed Adam 17$^{ex/ex}$ mice on Ldlr$^{-/-}$ background, then expanded on the previous studies of Holdt et al[9] and Canault et al[10] in Adam 17$^{ex/ex}$Ldlr$^{-/-}$ mice. The authors revealed that atherosclerotic plaque size at the aortic root was markedly increased in Adam 17$^{ex/ex}$Ldlr$^{-/-}$ mice compared with that of Adam 17$^{wt/wt}$Ldlr$^{-/-}$ mice (1.5-folds), which indicated that ADAM17 deficiency would promote atherosclerosis. They found no alteration of total, LDL, and HDL cholesterol levels in ADAM17-deficient mice, which suggested that ADAM17 may affect atherosclerosis progression independent of plasma lipid level. Considering the known function of ADAM17 as a metalloproteinase, they systematically screened currently known ADAM17 substrates and consistently observed reduced release of TNFR1 and TNFR2, both in the plasma of Adam 17$^{ex/ex}$Ldlr$^{-/-}$ mice and in the supernatant of Adam 17$^{ex/ex}$Ldlr$^{-/-}$ bone marrow–derived macrophages. Subsequently, they detected increased level of TNF-α and TNFR2, but not TNFR1 on the cell membrane of Adam 17$^{ex/ex}$Ldlr$^{-/-}$ macrophages compared with control macrophages, as well as elevated phosphorylation of bone marrow tyrosine kinase in chromosome X, a marker for constitutive activation of TNFR2 signaling. The proatherogenic effect of ADAM17 deficiency could be rescued by knockdown of TNFR2 in almost all of the vascular cells and macrophages detected. Finally, the authors detected less apoptotic cells and more proliferating macrophages in atherosclerotic lesions of Adam 17$^{ex/ex}$Ldlr$^{-/-}$ mice, which confirmed the in vitro results. Taken together, these data provide convincing evidence that ADAM17 deficiency and TNFR2 signaling activation promote atherogenesis in mice (Figure).

This is the first definitive study of global ADAM17 knockout in atherosclerosis by loss of function mouse model in LDL$^{-/-}$ background. Although the authors examined ADAM17-TNFR2 signaling in almost all of the cell types involving plaque formation, we must realize that ADAM17 expression and activity varies in different cell types on proatherosclerotic stimuli. Previous studies by generating myeloid cell lineage–specific knockout ADAM17 mice revealed reduced proinflammatory cytokines secretion.[14] Endothelial-specific knockout ADAM17 mice exhibited reduced pathological neovascularization which may affect plaque vulnerability.[16] Considering ADAM17 has >70 different substrates, shedding by ADAM17 in different cell types needs to be individually

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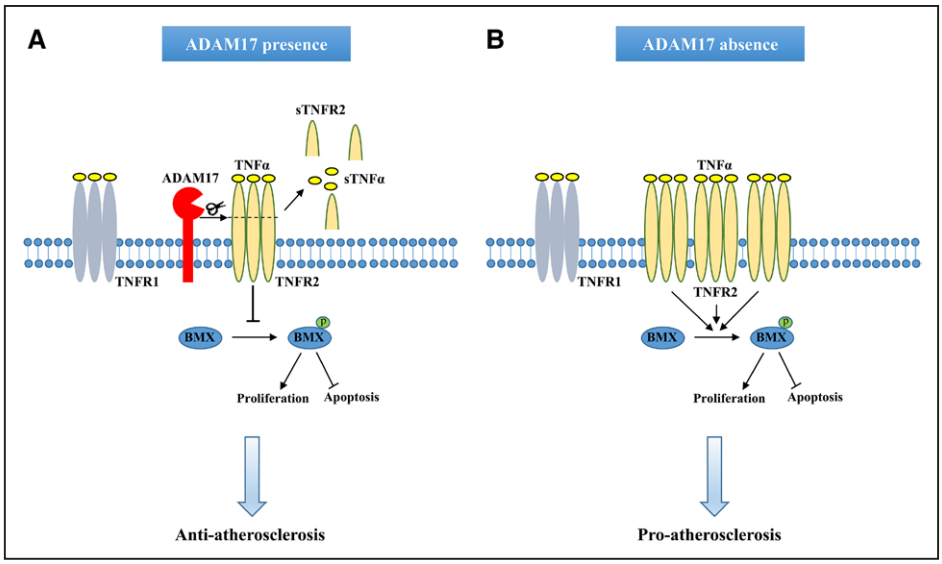

Figure. A, Protective role of a disintegrin and metalloproteinase 17 (ADAM17) in atherosclerosis. **B**, ADAM17 deficiency reduces shedding of tumor necrosis factor receptor 2 (TNFR2) and tumor necrosis factor-α (TNF-α), thereby promotes membrane TNFR2 accumulation and persistent TNFR2 signaling activation, and enhances the downstream antiapoptosis and proproliferation effects in macrophages and vascular smooth muscle cells. BMX indicates bone marrow tyrosine kinase in chromosome X; sTNF-α, soluble TNF-α; and sTNFR2, soluble TNFR2.

analyzed. Notably, recent development of novel proteomic methods may shed light on context-dependent bone fide substrates recognition.[17]

Overexpression of ADAM17 in atherosclerosis prone region raised the question how it is activated. Previous studies suggest that angiotensin II, reactive oxygen species, and polymethacrylate increase ADAM17 activity in multiple ways.[18–20] Inactive rhomboid types 1 and 2 have been reported to regulate forward trafficking of ADAM17 from endoplasmic reticulum to Golgi compartment where the prodomain of ADAM17 can be cleaved.[21] On the other hand, depletion of membrane cholesterol can induce ADAM17-dependent shedding.[22] More attention needs to be focused on the come and go of this ADAM17-TNFR2 axis. Additional studies are warranted to definitively demonstrate the role of ADAM17 in different cells and underlying regulatory mechanisms.

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Disclosures

None.

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