Atherosclerosis is a very complex pathology. Over the past two decades we have come to appreciate that a major component of this pathological process is chronic inflammation. This inflammatory state is not only characterized by infiltration of lipid laden macrophages, the hallmark cell of this disease, into the vascular wall, but also is characterized by the infiltration of a host of other inflammatory cells. The complex interaction of inflammatory cells with the normal residents of the vascular wall (ie, endothelial and smooth muscle cells) directs the progression of the disease. Inflammatory cells secrete a variety of chemokines and cytokines which have a profound effect on the development and progression of the plaque. Moreover, many of these cytokines can mediate both pro- and antiatherogenic processes depending on the cellular milieu. The tumor necrosis factor (TNF) and TNF receptor (TNFR) superfamilies encompass numerous cytokines and receptors suggested to play a pivotal role in atherogenesis. Although many members of these families such as TNF-α and CD40 ligand and their putative receptors are considered to be proatherogenic,1–4 studies have also demonstrated an antiatherogenic role for others, including the p55 TNFR.5 TNF-like weak inducer of apoptosis (TWEAK) and its putative receptor, fibroblast growth factor-inducible 14 (Fn14), are also members of the TNF and TNFR superfamilies, respectively. Both TWEAK and Fn14 have been detected in human atherosclerotic plaques, suggesting that these molecules may also play a role in the atherogenic process. Clinical data are controversial with studies demonstrating either a positive or negative correlation with an increased risk for cardiovascular events.6 Although many studies have examined the role of TWEAK and Fn14 in renal pathologies, to date there have been few mechanistic studies addressing their role in atherosclerosis. However, a recent study examined the role of cardiac function demonstrating that adenoviral over expression of TWEAK resulted in a dilated cardiomyopathy and cardiac dysfunction which was mediated by Fn14.7

See accompanying article on pages 2021 and 2061

In this issue of Atherosclerosis, Thrombosis, and Vascular Biology, data are presented from 2 different groups using different approaches, gain of function versus loss of function, to investigate the role of the TWEAK/Fn14 axis in the development and progression of atherosclerosis. Muñoz-Garcia and colleagues examined the effect of exogenous administration of human recombinant TWEAK on atherogenesis.8 In contrast, Schapira and colleagues used a TWEAK-inhibiting fusion protein, Fn14-FC, to block the biological function of TWEAK at Fn14.9 After feeding 12-week-old ApoE deficient (apoE−/−) mice a high-fat diet enriched in cholesterol for 4 weeks, Muñoz-Garcia et al injected mice with human recombinant TWEAK for 9 days to investigate the effect of TWEAK on early atherosclerotic lesion formation. This intervention resulted in a robust increase in atherosclerotic lesion formation compared to vehicle-treated controls. The increase in lesion formation was inhibited by pretreatment of mice with an antibody directed against TWEAK. To address the effect of TWEAK on advanced lesions, after feeding 16-week-old mice the same diet for 10 weeks, mice were injected with TWEAK for 9 days. Exogenous administration of TWEAK for 9 days also robustly increased lesion formation, which was again inhibited by pretreatment with an anti-TWEAK antibody. Both early and advanced atherosclerotic lesion formation was associated with TWEAK-mediated increases in inflammatory chemokines, RANTES and MCP-1, NFκB activation, and macrophage infiltration into the vascular wall, all of which were inhibited by pretreatment with the anti-TWEAK antibody. Although TWEAK administration increased CD4+ lymphocyte accumulation in advanced lesions, this effect was not blocked by pretreatment with the anti-TWEAK antibody. Interestingly, apoE−/− mice treated with the anti-TWEAK antibody alone had decreased macrophage, CD4+, and CD8+ lymphocyte infiltration into the vascular wall and decreased cytokine/chemokine production in both early and advanced lesions. However, atherosclerotic lesion area was only reduced when assessed at the advanced stage. Moreover, TWEAK only inhibited collagen formation in advanced stage lesion formation. Therefore, the authors proposed that TWEAK promotes this surprisingly robust increase in atherosclerotic lesion area in response to only 9 days of TWEAK treatment by increasing the inflammatory response in the vascular wall. However, it should again be noted that treatment with the anti-TWEAK antibody alone, which presumably inhibits endogenous TWEAK, attenuated the inflammatory response in the vascular wall in both early and advanced stage lesions, but only decreased lesion area when given during advanced stage of lesion formation. Shapira et al also used apoE-deficient mice to assess the role of the TWEAK/Fn14 axis in atherogenesis. Mice were injected IP twice weekly with Fn14-FC or an isotype control.
antibody from 5 to 17 weeks of age (early) or 17 to 29 weeks of age (delayed). Blockade of Fn-14 attenuated the development of plaques with an advanced phenotype during the early stage treatment group. In contrast to data presented by Muñoz-Garcia et al suggesting that TWEAK induced late stage lesion formation, Shapira et al demonstrated that blockade of TWEAK signaling through Fn14 did not inhibit lesion formation, but instead prevented the progression of lesions to a more advanced phenotype after delayed treatment with Fn14-FC. Moreover, Fn14 blockade also decreased fibrosis as evidenced by reductions in smooth muscle cell and collagen content in lesions in the delayed treatment group. Interestingly, inhibition of TWEAK signaling through Fn14 decreased CD45+ leukocyte content in initial plaques and increased macrophage cell number in the advanced plaques in the delayed treatment group; however, macrophages were of smaller size compared to control. In vitro studies demonstrated that blockade of TWEAK signaling through Fn14 did not alter macrophage apoptosis but inhibited oxidized lipid uptake into the macrophages, suggesting that blockade of TWEAK signaling through Fn14 may inhibit macrophage foam cell formation. While data presented by Muñoz-Garcia demonstrated that both endogenous and exogenous TWEAK promoted cytokine/chemokine production, blockade of TWEAK signaling through Fn14 had no effect on cytokine production. Taken together, Shapira et al suggest that TWEAK/Fn14 interactions do not prevent the development of plaques but impede the progression to a more advanced phenotype.

So what can we discern from these two studies? They both suggest that endogenous TWEAK participates in the atherogenic process. To date TWEAK is the only known ligand for Fn14, however recent data suggest that TWEAK is also a ligand for the scavenger receptor, CD163. Differences observed between these two studies could be attributed to TWEAKCD163-mediated effects, suggesting that TWEAK may mediate some of its effects through receptors other than Fn14. Fn14 activation results in TRAF-mediated activation of NFκB. Therefore, some of the differences observed could be attributed to the complexity of interactions in the NFκB signaling pathway especially in macrophages, which is evidenced by the interesting finding a number of years ago demonstrating that inhibition of NFκB signaling in macrophages increased atherosclerosis. Moreover, recent data suggest that TWEAK impairs NFκB activation of TNFR1 and proinflammatory signaling. These findings take us back to where we began and provide further evidence that members of TNF and TNFR superfamilies play a pivotal but complex role in the development and progression of atherosclerosis. Is TWEAK a novel therapeutic target for treatment of this disease? The jury is still out, and much is still left to learn about TWEAK and its receptors.

Disclosures
None.

References
Atherosclerosis: Should We Stop TWEAKing It?
Victoria L. King

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