Tumor Necrosis Factor Receptor and Ligand Superfamily Family Members TNFRSF14 and LIGHT
New Players in Human Atherogenesis

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Increasing evidence indicates that atherosclerosis is the consequence of complex, multifactorial processes involving the abnormal interplay between local mechanisms involved in lipoprotein metabolism, the extracellular matrix and coagulation proteins, endothelial and smooth muscle cells, mononuclear leukocytes, and growth factors/cytokines. A number of cytokines including those activating several members of the tumor necrosis factor (TNF) receptor superfamily have been consistently identified in atherosclerotic lesions and implicated in the pathogenesis of atherosclerosis. One of the earliest responses to hypercholesterolemia is an increase in the adherence of monocytes to arterial endothelium and then penetration into the intima. TNF-α together with interleukin (IL)-1β increases the adherence of leukocytes to endothelial cells, and in young ApoE-deficient mice, they promote monocyte accumulation within developing atherosclerotic lesions.

In established lesions, the actions and patterns of expression of TNF receptor superfamily (TNFRSF) members and their activating ligands is complex and, in most cases, seems to lead to the development of complex atherosclerotic lesions that are susceptible to rupture. TNFRSF members are defined as those structurally related to the first family members TNFR1 and TNFR2, (now TNFRSF1A and TNFRSF1B, respectively). Each member contains multiple copies of a cysteine-rich motif of approximately 40 amino acids that is known to provide the ligand recognition motif; their cytoplasmic regions are frequently capable of stimulating the transcription factors activator protein-1 and nuclear factor-κB. The latter factor is involved in regulating numerous genes critical for inflammatory responses, including IL-6, IL-8, vascular cell adhesion molecule-1, and E-selectin. A number of receptors also contain a “death domain,” which is associated with activation of apoptotic signaling pathways. Two receptors that elicit TNF-α responses, TNFRSF1A and TNFRSF1B, appear to mediate markedly different effects in atherosclerotic lesions despite the overall inflammatory properties exhibited by TNF-α. C57BL/6 mice lacking TNFRSF1A fed an atherogenic diet develop significantly larger lesions that those possessing receptors; upregulation of scavenger receptor activity on macrophages, resulting in greater numbers of foam cells without changes in plasma lipoproteins, appears to be responsible for the larger lesions. TNFRSF1B is highly expressed in human atherosclerotic lesions and colocalizes with smooth muscle alpha actin–positive cells and TUNEL-positive cells, suggesting some pro-apoptotic role in atherosclerosis; in vitro receptor activation induces vascular smooth muscle cell apoptosis.

TNFRSF5 (CD40) has also been implicated in atherosclerosis and is expressed by endothelial cells, smooth muscle cells, T-lymphocytes, and macrophages in lesions. Its ligand, TNFRSF5 (CD40L) is also constitutively expressed by these cells, and expression can be further elevated by exposing cells to IL-1β, TNF-α, or interferon-γ. CD40 ligation with CD40L induces vascular smooth muscle cells to express tissue factor. Its colocalization with CD40 on smooth muscle cells in atherosclerotic lesions suggests that CD40 may increase the thrombogenicity of inflamed lesions. CD40 ligation also activates IL-1β–converting enzyme (caspase-1) in vascular smooth muscle and endothelial cells, as well as increasing the secretion of a number of matrix metalloproteinases by endothelial cells and macrophages, gelatinase B (MMP-9), interstitial collagenase (MMP-1), and stromelysin (MMP-3), effects that can promote development of unstable lesions. Studies interrupting the CD40-CD40L system in vivo indicate similar effects in atherosclerosis. Preventing CD40 ligation with anti-CD40L antibodies in hyperlipidemic mice lacking the receptor for low-density lipoprotein reduces the size of developing aortic atherosclerotic lesions; lesion lipids, macrophages, and T-lymphocytes are all reduced by more than 50%. Whether disruption of CD40-CD40L signaling promotes regression of complex lesions is still unclear. However, the cellular composition of moderately advanced lesions in experimental animals is altered to contain greater numbers of smooth muscle cells, and collagen content is also increased. In humans, fatty streaks and advanced lesions contain elevated numbers of CD40-positive vascular smooth muscle cells and CD40-positive macrophages, consistent with postulated role of CD40 in the development and progression of atherosclerosis. Overall, the evidence that specific TNFR superfamily members and their ligands are involved in atherosclerosis is compelling.

In this issue of Arteriosclerosis, Thrombosis and Vascular Biology, Lee et al 18 present data that suggest the involvement of additional members of the TNF superfamilies of receptors and ligands in human atherosclerosis. Analyzing for TNFRSF14 (HVEM, TR2, LIGHT), they found this receptor to be present in regions rich in CD68-positive macrophage-de-
rived foam cells and HLA-DR-positive cells. LIGHT (TNFRSF14), its membrane-anchored ligand, was also present in atheromatous lesions and highest in regions rich in macrophage-derived foam cells. Although the cell types producing LIGHT were not identified, T-lymphocytes and macrophages are the most likely source.\textsuperscript{21,22} TNF-α was found to upregulate TNFRSF14 on monocytes, suggesting an interplay between TNF family members; receptor numbers were also greatly increased after monocyte-macrophage differentiation. TNFRSF14 is a single transmembrane protein originally cloned as a cellular mediator of herpes simplex virus entry (HVEM).\textsuperscript{20} It contains multiple TNFR-like cysteine-rich domains and a short cytoplasmic tail with some similarity to possible explanation for the lack of coexpression with TIMP-1 or TIMP-2 were present in these regions. One colocalized only with the three matrix metalloproteinases; no rich regions of lesions, TNFRSF14 expression induced THP-1 monocytes to produce interstitial collagenase contributing to lesion progression. TNFRSF14 stimulation also induced THP-1 monocytes to produce interstitial collagenase (MMP-1), gelatinase B (MMP-9), interstitial collagenase-3 (MMP-13), as well as TIMP-1 and TIMP-2. However, in foam cell–rich regions of lesions, TNFRSF14 expression colocalized only with the three matrix metalloproteinases; no TIMP-1 or TIMP-2 were present in these regions. One possible explanation for the lack of coexpression with TIMP-1 is IL-8, which downregulates TIMP-1 expression in cholesterol-loaded human macrophages.\textsuperscript{24} This mechanism could partially explain the imbalance between MMPs and TIMPs at these sites. Finally, TNFRSF14 does not possess the “death domain” present in the Fas and TNFRSF1A intracellular domains,\textsuperscript{22} suggesting that any TNFRSF14–mediated apoptosis in lesions would be indirect and at least in part dependent on elevating membrane-anchored TNF-α.\textsuperscript{25} The study carried out by Lee et al\textsuperscript{18} clearly establishes TNFRSF14 and LIGHT as integral components of the TNF cytokine-receptor systems present in human atherosclerotic lesions. As with other TNF receptor and ligand superfamilies, the actions of TNFRSF14 and LIGHT are likely to be complex and, as would be predicted from the structure of TNFRSF14, some effects are similar to those exerted by other TNFRSF members in atherosclerotic lesions. This is particularly so for macrophages and macrophage-derived foam cells.

Although TNFRSF14 expression in the human lesions is restricted to regions highly populated by macrophages, Lee et al\textsuperscript{18} indicate that LIGHT distribution is more diffuse, and though high in the macrophage-rich areas, it is present in more fibrous regions of lesions. While the significance of this latter observation was not examined, it raises the possibility that LIGHT might be influencing the functions of additional cell types in the lesions, possibly smooth muscle and/or endothelial cells. LIGHT also binds to TNFRSF5 (lymphotxin β receptor),\textsuperscript{5,26,27} which is expressed by some endothelial cells, epithelial cells, and several fibroblastic cell types,\textsuperscript{28,29} and a secreted decoy receptor TNFRSF6B.\textsuperscript{5,30} In addition to activating nuclear factor-κB–mediated gene transcription, LIGHT–induced clustering of TNFRSF3 can induce cell apoptosis by activating a TNF receptor–associated factor–3–dependent pathway.\textsuperscript{31} Additional information on TNFRSF3 and TNFRSF6B expression in human atherosclerotic lesions, as well as definition of the actions of all three TNF receptors for LIGHT in appropriate experimental animal models of atherosclerosis, should provide novel insights as to the significance of LIGHT and its receptors for the development and progression of atherosclerotic lesions.

References


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