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.

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rived foam cells and HLA-DR-positive cells. LIGHT (TNFRSF14),\(^5\) 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.\(^{19}\) TNF-\(\alpha\) 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).\(^{20}\) It contains multiple TNFR-like cysteine-rich domains and a short cytoplasmic tail with some similarity to TIMP-1. It is expressed in a variety of tissues with particularly high expression in T- and B-lymphocytes and monocytes.\(^{21,22}\)

CD40. It is expressed in a variety of tissues with particular intracellular domains,\(^{22}\) suggesting that any TNFRSF14-mediated apoptosis in lesions would be indirect and at least in part dependent on elevating membrane-anchored TNF-\(\alpha\).\(^{23}\) The study carried out by Lee et al.\(^{18}\) 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 superfamily members, 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.\(^{18}\) 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 (lymphotixin \(\beta\) receptor),\(^{5,26,27}\) which is expressed by some endothelial cells, epithelial cells, and several fibroblast cell types,\(^{28,29}\) and a secreted decoy receptor TNFRSF6B.\(^{5,30}\) In addition to activating nuclear factor-\(\kappa\)B-mediated gene transcription, LIGHT-induced clustering of TNFRSF3 can induce cell apoptosis by activating a TNF receptor–associated factor-3–dependent pathway.\(^{31}\) 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


Tumor Necrosis Factor Receptor and Ligand Superfamily Family Members TNFRSF14 and LIGHT: New Players in Human Atherogenesis
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Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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