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Notă: p.72:00 semnifică textul de la pag.72 până la finele paginii.

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Thematic review series: The Immune System and Atherogenesis

Cytokine regulation of macrophage functions in atherogenesis

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Abstract This review will focus on the role of cytokines in the behavior of macrophages, a prominent cell type of atherosclerotic lesions. Once these macrophages have immigrated into the vessel wall, they propagate the development of atherosclerosis by modifying lipoproteins, accumulating intracellular lipids, remodeling the extracellular environment, and promoting local coagulation. The numerous cytokines that have been detected in atherosclerosis, combined with the expression of large numbers of cytokine receptors on macrophages, are consistent with this axis being an important contributor to lesion development. Given the vast literature on cytokine-macrophage interactions, this review will be selective, with an emphasis on the major cytokines that have been detected in atherosclerotic lesions and their effects on properties that are relevant to lesion formation and maturation. There will be an emphasis on the role of cytokines in regulating lipid metabolism by macrophages. We will provide an overview of the major findings in cell culture and then put these in the context of in vivo studies.—Daugherty, A., N. R. Webb, D. L. Rateri, and V. L. King. **Cytokine regulation of macrophage functions in atherogenesis.** ***J. Lipid Res.*** **2005.** 46: **1812–1822.**

Supplementary key words lipoprotein • modification • metabolism • matrix • coagulation

As noted in Getz's overview (1), lesions contain large numbers of cytokines that can be derived from several cell types. These cytokines may affect the function of many cell types in atherogenesis. The effects of cytokines on endothelial and smooth muscle cells are discussed in Raines and Ferri's contribution to this series (2). The purpose of this review is to focus on the effects of cytokines on macrophages in the evolution of atherosclerotic lesions. This is a vast literature that has necessitated some selectivity in the areas that can be covered. Given the subject area of this journal, we have elected to focus particular attention on the effect of cytokines on lipid metabolism in macrophages.

MACROPHAGE FUNCTIONS IN ATHEROSCLEROTIC LESIONS

Macrophages are hypothesized to be attracted to the subendothelial space to remove noxious materials deposited at atherosclerosis-prone regions of arteries. The precise chemical identity of the substance that attracts macrophages has not been unequivocally defined, although many candidate molecules are components of modified lipoproteins (3, 4). However, the function of infiltrating cells becomes subverted and leads to their retention within the subendothelial space. In this region, it is proposed that macrophages modify adjacent lipoproteins while also providing major mechanisms of removal for modified materials from the extracellular environment. The combination of lipoprotein modification and uptake leads to macrophages becoming engorged with lipids and resulting in a morphology that is given the descriptive name of "foam cells." Lipid engorgement causes pronounced cellular hypertrophy, with the cell diameter being >10 times that of the originating monocyte. Probably as a result of the immense size increase, lipid-laden macrophages are chronically entrapped in the subendothelial space. Trapped macrophages can then invoke processes that perpetuate the continual recruitment of monocytes, leading to an expanded lesion volume. In addition, the subendothelial macrophages can influence the behavior of neighboring cell types within atherosclerotic lesions.

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Abbreviations: apoE, apolipoprotein E; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LOX-1, lectin-like oxidized low density lipoprotein receptor-1; LRP, low density lipoprotein receptor-related protein; M-CSF, monocyte colony-stimulating factor; MMP, matrix metalloproteinase; SR-A, class A scavenger receptor; SR-BI, scavenger receptor class B type I; TGF, transforming growth factor; TNF, tumor necrosis factor.

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LPL in human monocyte-derived macrophages from early to late stages of culture (38, 39) and by transcriptional regulation (40). Macrophage LPL expression is also inhibited by transforming growth factor (TGF)-β through a transcriptional effect (41, 42), but it is upregulated by tumor necrosis factor (TNF)-α (43). Thus, there is substantial evidence that cytokine regulation may be an important contributor to the atherogenic effects of macrophage-expressed LPL. Although LPL can modify specific lipoprotein fractions, it is possible that nonlipolytic properties of the protein are responsible for its effects in atherogenesis (44).

CYTOKINE REGULATION OF LIPOPROTEIN ENTRY INTO MACROPHAGES

One of the most prominent changes in macrophages after entry into the subendothelial space of developing atherosclerotic lesions is the engorgement of these cells with lipid. Intracellular lipid stores are initially formed with simple droplet morphology. With progressive lipid engorgement, there is the formation of intracellular complexes of cholesterol and phospholipid and cholesterol crystals (45, 46). These complexes and crystals are frequently encased by an acid phosphatase-positive layer, consistent with entrapment in lysosomes or late endosomes.

It is now recognized that many receptors are present on macrophages that bind a wide range of native and modified lipoproteins. Several major receptor types that recognize native lipoproteins may be regulated by cytokines in macrophages. LDL receptors have a clearly defined role in the cholesterol homeostasis of the whole body. Their role in macrophages has not been explored widely because of the assumption that they are downregulated in lipid-laden lesional macrophages. However, LDL receptor protein is detectable in experimental atherosclerotic lesions (47, 48). Furthermore, macrophage LDL receptors influence atherogenesis under conditions of modest hyperlipidemia (48, 49). The expression of LDL receptors on macrophages in cultured cells is a function of the origin and differentiation status (50). Macrophage LDL receptors have been demonstrated to be upregulated and downregulated by IFN-γ and TGF-β, respectively (41, 51). Expression of LDL receptors may also have implications on the mode of metabolism of the highly atherogenic lipoprotein fraction, β-VLDL, which may have characteristics similar to those of postprandial chylomicron lipoproteins (48, 49).

In addition to LDL receptors, β-VLDL is also recognized by VLDL receptors. This receptor type is also expressed on macrophages and is downregulated by IFN-γ (52). The functional significance of this downregulation can be shown by the inhibition of β-VLDL-induced foam cell formation by IFN-γ.

Another lipoprotein receptor type that recognizes native lipoproteins is the low density lipoprotein receptor-related protein (LRP; also designated CD91) (53, 54). Although the embryonic lethality of LRP-deficient mice has impeded a full characterization of its function, its properties appear consistent with being the major system for the clearance of chylomicron remnants from the plasma (54). LRP on macrophages has consistently been shown to be downregulated in the presence of IFN-γ (55–57). Conversely, TGF-β upregulates macrophage LRP, whereas M-CSF has no effect (56). These changes in macrophage LRP expression may have implications for lipoprotein accumulation within lesional macrophages. LRP, which is also termed the α2 macroglobulin receptor, has a wide range of ligands in addition to lipoproteins (54). Many of these ligands are responsible for regulating the extracellular proteolytic environment of macrophages (58).

Although there has been limited work on the cytokine regulation of native lipoprotein receptors, there has been considerable effort to study the cytokine regulation of receptors for modified lipoproteins. As discussed in the preceding section, there are several mechanisms of lipoprotein modification that can be regulated by cytokines. Many of these modifications involve some form of oxidative damage. The original receptor for modified lipoproteins was designated a "scavenger receptor" based on its ability to mediate the endocytosis of acetylated LDL (59). There are now many proteins that have been designated as scavenger receptors that are broadly classified by gross structural characteristics in an alphabetic system (8).

The initially discovered scavenger receptor is now referred to as class A scavenger receptor (SR-A) (60). This receptor is able to transport acetylated and oxidized forms of LDL into macrophages by a process that is not downregulated by intracellular cholesterol content (61). Several studies have used genetically manipulated mice to define the effect of SR-A on atherosclerotic lesion formation (62). The ability of cytokines to regulate the SR-A receptor has been the subject of many publications, of which some selected examples are summarized in **Table 1**. IFN-γ is the most widely investigated cytokine. Earlier studies demonstrated a downregulation of SR-A by IFN-γ in human monocyte-derived macrophages (63, 64). IFN-γ has also been reported to inhibit SR-A at the transcriptional level (65). Decreased foam cell formation occurs by the incubation of IFN-γ with modified lipoprotein and macrophages (64). These effects, combined with studies on smooth muscle proliferation (66, 67), suggest that IFN-γ may reduce the atherogenic process. However, there are also reports of IFN-γ having other effects on SR-A activity, protein, and transcription that are either neutral or inhibitory (27, 68, 69). Markedly different results have also been reported for GM-CSF, which has shown both upregulation and downregulation of SR-A activity by this cytokine (27, 70). These differing responses may be a reflection of the heterogeneity of macrophages, which may lead to differences in the phenotype of the cultured cells. Consistent with this theme, IFN-γ increases SR-A expression in the early differentiation phase of blood-borne monocytes or the human cell line THP-1, but it downregulates this receptor in mature macrophages (69). These conflicting findings may also be related to the mode of data representation, because both IFN-γ and GM-CSF may markedly increase cellular protein content without influencing cell

Conversely, TGF-β1 increased ABCA1 expression and cholesterol efflux (41, 105, 113), although the binding of HDL was decreased by this cytokine (85).

Cytokines have many effects on macrophages with regard to intracellular cholesterol metabolism and its consequences on sterol efflux. With few anomalies, the most extensively studied cytokine, IFN-γ, increases intracellular cholesterol storage when cells are not incubated with modified lipoproteins. Further studies to demonstrate whether these changes affect macrophage viability would be of interest (98).

CYTOKINE REGULATION OF THE EXTRACELLULAR MATRIX OF MACROPHAGES

The extracellular matrix of the artery contains many different proteins. The subendothelial region contains type IV collagen, laminin, and fibronectin. The integrity of extracellular matrix proteins in atherosclerotic lesions may be compromised by a large number of enzymes, most of which belong to the matrix metalloproteinease (MMP), cysteine protease, or serine protease families.

Many MMPs have been detected in atherosclerosis, although the dominant MMPs expressed by macrophages that have been implicated in lesion development are MMP-9 and MMP-12. Of these MMPs, only MMP-9 has been shown to alter the atherogenic process with its deficiency, reducing lesion size in several vascular areas (114). Moreover, this study demonstrated that bone marrow-derived stem cells were a significant source of the MMP-9 that modulates atherogenesis.

The Th2 cytokines IL-4 and IL-10 attenuated MMP-9 expression and activation in peripheral blood monocytes, mouse peritoneal macrophages, and human alveolar macrophages (115–117). Activation of MMP-9 is tightly regulated by tissue inhibitor of MMP-1, which is markedly upregulated by IL-10 (117, 118). TGF-β decreases lipopolysaccharide-induced MMP-9 expression and activation in cultured MM6 and RAW 264.7 cells (119). Conversely, TNF-α upregulated MMP-9 in human peripheral blood monocytes and peritoneal macrophages (120, 121). However, the effect of IFN-γ on the regulation of MMP-9 is unclear, with some studies demonstrating that it upregulates MMP-9 in mouse peritoneal macrophages and others suggesting that it downregulates MMP-9 (122–125).

CYTOKINE REGULATION OF COAGULATION IN ATHEROSCLEROSIS

The presence of tissue factor in atherosclerotic lesions is proposed to exert a major effect on the development of atherosclerosis complications at late stages of the disease (126). Tissue factor is expressed in all of the major cell types of atherosclerotic lesions, with a preponderance in macrophages (127, 128). Tissue factor expression in cultured macrophages is downregulated by the Th2 cytokines IL-4, IL-10, and IL-13, whereas the Th1 cytokine IFN-γ has the opposite effect (129, 130). Some of the effects on tissue factor expression, particularly those of IFN-γ, are differentiation-specific (131, 132). Overall, there is limited information regarding the role of cytokine-macrophage interactions on the effect of coagulation responses in atherosclerotic lesions.

EXTRAPOLATION OF CYTOKINE EFFECTS ON CULTURED CELLS TO THE ATHEROGENIC PROCESS IN VIVO

There have been numerous studies to determine the role of specific cytokines in the development of atherosclerosis. As described above, one cytokine that has been studied extensively in cell culture studies is IFN-γ, which is also one of the more extensively investigated cytokines in in vivo studies of atherogenesis. Studies with cultured cells have demonstrated many effects of IFN-γ on the intracellular accumulation of lipids in macrophages. These findings lead to the notion that IFN-γ would retard atherosclerosis, especially by minimizing intracellular lipid accumulation in macrophages. However, there are conflicting results in cultured cells. In contrast, the effects of IFN-γ on the development of atherosclerosis in mouse models of the disease have been quite consistent, but they have contradicted the original concept of IFN-γ being antiatherogenic. Thus, deletion of both IFN-γ and its receptor decreased the size of atherosclerotic lesions in apoE-deficient mice (133, 134). Deletion of IFN-γ also decreased the size of atherosclerotic lesions in LDL receptor-deficient mice (135). Conversely, exogenous administration of IFN-γ or its upstream regulators, IL-12 or IL-18, increased the extent of atherosclerosis (136–138). Currently, the only published report suggesting an antiatherogenic role for IFN-γ comes from a study of irradiated LDL receptor-deficient mice that were repopulated with cells from IFN-γ-deficient mice. Under these conditions, the absence of IFN-γ in bone marrow-derived stem cells increased the size of lesions in three different vascular regions (139).

Although gene manipulation and exogenous cytokine administration have provided valuable insight into the atherogenic process, these do not localize the effect to a specific action of the cytokine on macrophages. One mode of focusing on cytokine-macrophage interactions is to use mice that are deficient in specific cytokine receptors. Previous studies have used the technique of bone marrow transplantation as a mode of determining a leukocyte-specific role in atherosclerosis (140, 141). This approach has been used in the chemokine field, for example, in studies using CCR2 and CXCR-2 (142, 143). However, bone marrow transplantation studies with cytokine receptor-deficient mice have not been performed to date. Although such studies provide valuable insight, their interpretation should be tempered by the potential for bone marrow-derived stem cells to differentiate beyond myeloid and lymphoid lineages (144, 145). Thus, the definition of an interaction of a macrophage with a specific

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cytokine as a functionally significant event in atherogenesis will be facilitated by the ability to specifically regulate cytokine receptors in this cell type.

CONCLUSIONS

The macrophage is a pivotal cell type throughout the initiation and maturation of atherosclerotic lesions. The combination of the many cytokines present in atherosclerotic lesions and the abundant cytokine receptors on macrophages is consistent with an important role of cytokine-macrophage interactions in lesion development. However, the abundance of both cytokines and receptors on macrophages also provides some challenges to unequivocally determining the relative importance and mechanism of a specific cytokine. The most obvious road ahead is the use of molecular engineering to enable the ablation and enhancement of cytokine responses in macrophages. With the increasing identification of specific cytokine receptors, coupled with evolving modes of altering gene expression in macrophages (146, 147), it is likely that this will spawn many studies to elucidate the role of cytokine interactions with macrophages.

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