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Commentary

The role of T lymphocytes in inflammation

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Lymphocytes, together with monocyte-derived macrophages, are common participants in inflammatory responses associated with various forms of tissue injury, ranging from normal wound repair to the inflammatory–fibroproliferative response associated with the advanced lesions of atherosclerosis. Until relatively recently, the association of both $CD4^+$ and $CD8^+$ T lymphocytes with these various inflammatory–fibroproliferative responses, although noted by numerous investigators, has remained poorly understood (1–4). In some instances, it has been assumed that the presence of T lymphocytes signifies some form of immune response in association with the tissue injury. Thus, T cells may enter the lesion in response to plaque neoantigens against which the individual has not yet acquired tolerance (4). On the other hand, it has been suggested that their presence may simply reflect a nonspecific association.

Unlike monocyte-derived macrophages, the principal function of T lymphocytes has not been considered to be phagocytic or secretory, but rather to be to produce limited numbers of secreted molecules, and primarily to be involved in cell–cell interactions. Substances such as γ-interferon and, more recently, several cytokines have been thought to represent the limited repertoire of molecules potentially formed by T cells. In the report by Blotnick *et al.* (5), appearing in this issue, convincing evidence is presented to demonstrate that T cells produce two relatively potent growth-regulatory molecules—namely, some form of heparin-binding epidermal growth factor-like growth factor (HB-EGF), an apparently secreted form of basic fibroblast growth factor (FGF), a molecule which does not normally have a signal sequence and, thus, is not thought to be secreted by the classical secretory pathway. Although it is not clear that the form of basic FGF released by the T lymphocytes demonstrated in this study is similar to several of the known forms of FGF that do have signal peptides, the secretion of two such potent growth factors adds a new dimension to the potential role of T lymphocytes not only as components of the immune inflammatory response but also as, perhaps equally important, antecedents of the fibroproliferative response associated with inflammation. The production of growth-regulatory molecules and cytokines by T cells clearly affords opportunities for T cell–nonimmune cell interactions.

In the case of atherosclerosis, both $CD4^+$ and $CD8^+$ T lymphocytes have been shown to be common components of all phases of the lesions present, not only in experimental animals, such as nonhuman primates, but in human lesions in every stage of development (1, 4). Unlike the lesions of atherosclerosis associated with graft rejection after heart transplant, which are symmetrical and contain extraordinarily large numbers of both types of T lymphocytes as well as monocyte-derived macrophages (much greater than those found in the lesions of common atherosclerosis), the presence of $CD4^+$ and $CD8^+$ cells and their possible secretory products in the lesions of common atherosclerosis raises new possibilities to be considered regarding the role of T lymphocytes in the process of atherogenesis. The question of the potential antigens that may be responsible for T lymphocyte–macrophage interactions still remains unanswered. However, the role of the lymphocyte, not only in terms of its potential interactions with monocyte-derived macrophages within these inflammatory responses, but in numerous other potentially important disease processes, must now be raised in relation to the possibility that T lymphocytes affect the fibroproliferative response in ways that had not previously been considered.

The identification of the two growth-regulatory molecules reported by Blotnick *et al.* (5) represents a somewhat surprising observation. HB-EGF is an extremely potent mitogen for cells that contain EGF receptors and, in particular, for smooth muscle cells potentially involved in the process of atherogenesis. HB-EGF can be secreted by activated monocyte-derived macrophages (6) and by smooth muscle cells (7, 8) but has not heretofore been reported to be secreted by T cells. What factors *in vivo* could be responsible for the expression of the HB-EGF gene in these cells? Is the gene expressed *in vivo* during atherogenesis? Does antigen recognition by appropriate T cells induce expression of the gene? These and other questions raise intriguing possibilities concerning both the role of T cells in atherogenesis and the importance of this growth factor in this process.

As to basic FGF, the evidence suggesting that this molecule is secreted by T cells is equally surprising, unless a modified secretory form of the molecule is expressed by the T cells. The data for both growth factors are intriguing and cast the T cells in a potentially new role, raising questions concerning T cell–macrophage and T cell–smooth muscle interactions in atherogenesis.

Thus, the report by Blotnick *et al.* (5) stimulates one to reconsider the role of the T lymphocyte as a secretory cell in wound healing and in the inflammatory–fibroproliferative responses associated with injury to tissues, such as in liver cirrhosis, in rheumatoid arthritis, and in atherogenesis (9). It remains to be demonstrated whether T lymphocytes actually express the genes for these growth factors in the various disease processes *in vivo* and whether or not the protein is actually synthesized and secreted *in vivo* by these cells.

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