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T CELL SIGNALING OF MACROPHAGE FUNCTION IN INFLAMMATORY DISEASE

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1. ABSTRACT

Macrophages play diverse roles in episodic T cell-mediated inflammatory diseases such as multiple sclerosis and rheumatoid arthritis, function as accessory cells for T cell activation, as pro-inflammatory cells, as effector cells which mediate tissue damage, and as anti-inflammatory cells which promote wound healing. In addition to the many roles of T cell-derived cytokines in differentially modulating these diverse macrophage activities, research over the last few years has demonstrated that contact-dependent signaling which occurs during T cell-macrophage adhesion is a critical triggering event in the activation of macrophage function. Substantial research emphasis has been placed on CD40 as a mediator of contact-dependent signaling. However, other membrane-anchored receptor:ligand pairs may also contribute to the stimulation of macrophage function. This is a brief review of the rapidly expanding, but still incomplete, knowledge of how T cells, through both contact-dependent and cytokine signals, regulate macrophage function during inflammatory disease.

2. INTRODUCTION

Research over the past decade has only begun to unravel the complex interactions between T cells and macrophages that are involved in the pathogenesis of cell-mediated inflammatory diseases such as multiple sclerosis. The cellular infiltrates of active sclerotic lesions include CD4+ T cells (Th1 with some Th0 and Th2), CD8+ T cells, and macrophages (microglia and monocytes) (1-8). The types of cells present reflect the state of progression of the inflammatory lesion. Macrophages play critical accessory, inflammatory, and effector roles in this non-septic T cell-mediated inflammatory disease (5-9) and tend to be present throughout the inflammatory process. The development of a cell-mediated response is currently hypothesized to depend on the differentiation of interferon (IFN)-gamma producing Th1 cells from activated Th0 precursors (10,11). The production of interleukin (IL)-12 by macrophages clearly plays an important role in the maturation of Th1 cells (10). Upon maturation, these Th1 cells, as well as inflammatory CD8+ cells, both of which produce IFN-gamma and tumor necrosis factor (TNF)-alpha/beta, play a dominant role in macrophage activation and pathogenesis of the inflammatory lesion (1,3,12-15). In contrast, IL4/IL10-producing T cells are hypothesized to play a role in down-regulation of the inflammatory response (1,3,16). It is these “type 2” CD8+ cells that appear to be active in the cellular infiltrate of sclerotic lesions that are in remission (1,3).

In addition to the many roles of T cell-derived cytokines in stimulation and inhibition of macrophage function (13), research over the last few years has demonstrated that the critical triggering event in activation of macrophage cytokine production and effector function is contact-dependent signaling during T cell:macrophage adhesion (17-24). Substantial research emphasis was placed on CD40 as a mediator of contact-dependent

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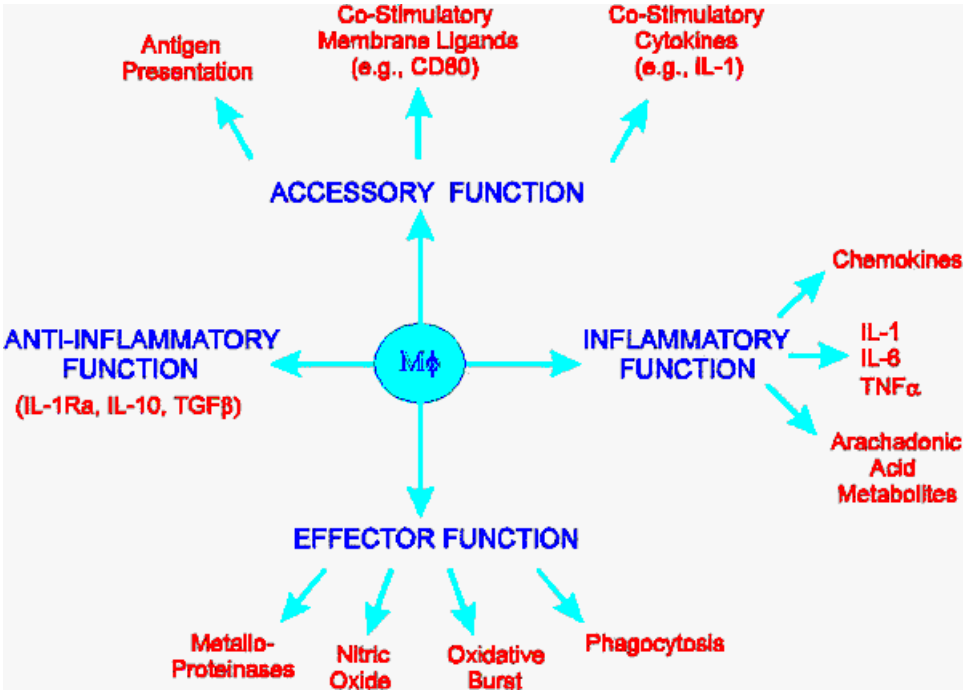

Figure 1. The diverse functions of macrophages. Macrophages are capable of many functional activities and contribute both to the initiation of cell-mediated immune response and to the effector limb of those responses. During the course of the response, macrophages can display, at different times, both inflammatory and anti-inflammatory activities.

signaling of macrophages. CD40 ligation has been reported to contribute to the induction of accessory molecules such as CD80 and CD86 (25-27), to the induction of inflammatory cytokines and chemokines (27-29), and to the induction of nitric oxide generation (24) and metalloproteinase secretion (30). However, the observation that T cells from CD40L-deficient mice are capable of contact-dependent signaling of macrophages (31) establishes that membrane-anchored receptor:ligand pairs other than CD40:CD40L can be involved in T cell signaling of macrophages. In the following sections, we try to provide a succinct account of T cell signaling of macrophages which, although brief and simplified for the sake of clarity, emphasizes the complexity of the cascading cell-cell interactions involved in a relapsing inflammatory autoimmune disease.

3. MULTIPLE ROLES OF MACROPHAGES IN INFLAMMATORY DISEASES.

The cellular infiltrates of active sclerotic lesions are dominated by cells of the monocytic lineage (macrophages and microglial cells) (6-8). These macrophages can display very diverse functions in sclerotic lesions (Fig. 1). They can function as accessory cells, presenting antigen and providing co-stimulatory ligands (e.g., CD80, CD86, and CD48) and co-stimulatory cytokines (e.g., IL-1 and IL-12) to the infiltrating T cells (10,13,32-36). Macrophages can be activated to produce prodigious amounts of pro-inflammatory cytokines such as TNF-alpha, IL-1, and IL-6, chemoattractant cytokines such as IL-8 and macrophage inflammatory protein (MIP)-1 alpha/beta (13,37), and pro-inflammatory products of arachidonic acid metabolism (13,38).

TNF-alpha, in particular, appears to play a critical role in the pathogenesis of experimental allergic encephalomyelitis, the murine model of multiple sclerosis, insofar as administration of anti-TNF-alpha antibodies *in vivo* inhibits the development of experimental allergic encephalomyelitis (39).

Interestingly, in addition to the inflammatory and destructive activities listed above, macrophages have the potential to contribute to the remission of the inflammatory episode, although the degree to which they participate in remission has not yet been directly assessed. Macrophages can be induced to generate toxic reactive oxygen and nitrogen intermediates(13,40-45) and to secrete "tissue restructuring" metalloproteinases (13,46-48), each of which have been hypothesized to directly contribute to the demyelinization process (49-51). Macrophages also can be induced to secrete cytokines which inhibit macrophage accessory, inflammatory, and effector functions. IL-10, which is produced by both macrophages and T cells, down-regulates

expression of costimulatory molecules such as CD86 (52,53), inhibits the production of IL-1 and TNF-alpha and reduces generation of reactive oxygen and nitrogen intermediates (54-57). Transforming growth factor-beta (TGF-beta), which is produced by many cell types including macrophages and T cells, also inhibits generation of reactive oxygen and nitrogen intermediates (58,59), especially in synergy with IL-10 (43,57,60), and is hypothesized to play a critical role in resolution of inflammatory lesions in experimental allergic encephalomyelitis (61-63).

4. MECHANISMS OF T CELL-MEDIATED INDUCTION OF MACROPHAGE FUNCTIONS.

The induction of these diverse macrophage functions is complex, differentially regulated, and poorly understood. Cytokines can stimulate or inhibit many of the macrophage functions described above but the modulating effect of many of the cytokines depends on the state of activation of the target macrophage population, the triggering signal, and timing (13,64,65). Although some exceptions have been noted, T cell cytokines such as IFN-gamma, IL-4, GM-CSF, and IL-3 generally can enhance accessory and co-stimulatory activity (13,29,66-69) and IFN-gamma, GM-CSF, and IL-3 can augment oxidative burst capacity (70-73). The combination of IL-2 plus IFN-gamma has been shown to induce TNF-alpha production and the combination of TNF-alpha and IFN-gamma have been shown to induce nitric oxide production (74-79). Thus, cytokines, especially the Th1 cytokines (IL2, TNF-alpha, IFN-gamma), can stimulate inflammatory and tissue destructive activities in macrophages.

In contrast, IL-10, TGF-beta, and, to a lesser degree, IL-4 (Th2 cytokines) inhibit the induction of oxidative burst and nitric oxide generation (54,57-59,80) and inhibit inflammatory cytokine production by macrophages (54-56,61,81), but do not affect (or enhance) IL-1Ra (IL-1 Receptor antagonist), IL-10 and TGF-beta production (61,82,83). Thus activated macrophages modulated by TGF-beta may display predominantly anti-inflammatory activities, such as secretion of IL-1Ra, IL-10, and TGF-beta.

Although these cytokines play an important role in modulating macrophage function, it is now clear that a critical mechanism by which T cells trigger these macrophage functions involves engagement of membrane-anchored receptor:ligand pairs during heterotypic adhesion between T cells and macrophages. Macrophage accessory, inflammatory, effector, and inhibitory functions have all been shown to be stimulated by paraformaldehyde fixed activated T cells or plasma membranes isolated from activated T cells (13,17-24,44,45,47). In each of these systems, pre-activation of the T cells is a requirement for cell contact-dependent signaling, suggesting the involvement of activation-induced membrane-anchored ligands on the T cells.

5. CONTACT-DEPENDENT SIGNALING OF MACROPHAGE ACTIVATION.

CD40:CD40L is the receptor:ligand pair that has received the most attention in the context of contact-dependent signaling of B cells and macrophages (34,84-87). CD40L is expressed transiently upon activation of T cells, with maximum expression usually observed at 5-10 hrs (88,89). Anti-CD40L antibody interferes with T cell signaling of macrophage accessory function, cytokine production and nitric oxide generation (24,25,28). Conversely, anti-CD40 antibody (28), CD40L-transfected cells (29), or soluble trimeric CD40L (27) induce expression of accessory molecules and production of a full array of cytokines (IL-1, TNF-alpha, IL-6, IL-10, IL-12) by macrophages. However, although anti-CD40L antibody nearly completely blocks induction of IL-1 release and CD80 expression by isolated T cell membranes or fixed T cells (25,28), it only partially blocks nitric oxide generation and CD86 expression (24,25). These observations suggested that CD40 ligation is not solely responsible for T cell contact-dependent signaling. This was confirmed by the observation that T cells from CD40L-deficient mice can activate macrophage nitric oxide generation via contact-dependent signaling (31). Although CD40L-deficient T cells, paraformaldehyde-fixed after being activated for 5 hrs on anti-CD3, lacked the ability to signal macrophage nitric oxide production, CD40L-deficient T cells, fixed after being activated for 24 hrs on anti-CD3, were able to signal macrophage nitric oxide production as effectively as similarly activated normal T cells (31). This indicates that CD40 ligation may dominate signaling early in T cell-macrophage interaction but that other receptors may become involved later in the interaction.

Receptors other than CD40 that have been reported to signal macrophage function include CD23 (90,91), CD31 (92), CD38 (93), CD44 (94), CD45 (45,94), CD69 (95,96), and LFA-3 (94). The most abundant data is on CD23. CD23 is the low affinity Fc RII and thus is capable of binding complexes of antigen and IgE antibody. In addition, CD23 binds CD21 (97) and, according to one report, also binds CD11b and CD11c (98). Ligation of membrane CD23 on macrophages induces production of TNF-alpha, IL-6, and nitric oxide (97,99,100). Interestingly, ligation of CD21 on the macrophage membrane by soluble CD23 also has been reported to induce the production of TNF-alpha and IL-1 by macrophages (101,102). CD21 (90) and, under more restricted conditions, CD23 (103) have been reported to be expressed by activated but not by resting T cells. It is therefore possible that the CD23:CD21 receptor:ligand pair is

Table 1
The Roles of CD40:CD40L Interactions in Cell-Mediated Inflammatory Disease

Interacting Cell	Functions Induced	Role in Inflammatory Response
Dendritic Cells	CD80 Expression IL-1 Production	Stimulation of Immune Response
Histiocytes, Monocytes	IL-12 Production	Development of Th1 Cells
Histiocytes, Monocytes	Inflammatory Cytokine Production	Enhancement of Inflammatory Response
Vascular Endothelial Cells	Homing/Adhesion Molecule Expression (e.g., VCAM)	Enhanced Recruitment of T Cells into Inflamed Tissue
Monocytes/Macrophages	Production of NO, O_3^-, and metalloproteinases	Tissue Destruction
Macrophages/fibroblasts	Production of TGF-beta/Proliferation	Tissue Repair/Remission

Ligation of CD40 on myeloid cells, endothelial cells, and fibroblasts can induce a wide range of functional activities which could contribute to essentially every aspect of cell-mediated inflammatory responses.

involved in T cell-mediated signaling of some inflammatory macrophage functions.

6. ROLE OF CONTACT-DEPENDENT SIGNALING IN AUTOIMMUNE DISEASE.

The role of contact-dependent signaling in the development of experimental allergic encephalomyelitis has been shown dramatically using transgenic B10.PL mice expressing the T cell receptor reactive with the encephalitogenic peptide (Ac1-11) of myelin basic protein. Transgenic CD40L-deficient mice, unlike +/+ transgenic mice, do not develop acute experimental allergic encephalomyelitis upon immunization with Ac1-11 (104). This nonresponsiveness was ascribed to the inability of CD40L-deficient T cells to induce CD80 expression on dendritic cells. The adoptive transfer of CD80-positive accessory cells into CD40L-deficient mice restored their ability to respond to antigen and to develop experimental allergic encephalomyelitis. This indicates that, unless an undiscovered second ligand for CD40 exists, T cells are capable of driving the inflammatory process by CD40-independent receptor:ligand and/or cytokine signaling.

Although the above studies with transgenic CD40L-deficient mice suggest that CD40 ligation is not *required* for the development of sclerotic lesions once the CD80 costimulus is provided, studies with normal animals indicate that CD40:CD40L interactions play a significant role throughout the inflammatory process. Administration of anti-CD40L antibody as late as 7-9 days after immunization of SJL mice with encephalitogenic peptide reduced the extent and severity of lesions by more than 50% (6). This is not surprising because CD40:CD40L interactions are known to play many roles in cell-mediated inflammatory responses, including stimulation of expression of adhesion and homing molecules on vascular endothelium, stimulation of chemokine and inflammatory cytokine production, stimulation of the production of IL-12, which is critical for maturation of the inflammatory Th1 subset, and stimulation of fibroblasts (105) (Table 1). Several of the above activities are critical for the development of experimental allergic encephalomyelitis. VCAM-1 plays a critical role in the inflammatory process of experimental allergic encephalomyelitis (106); ligation of CD40 on endothelial cells induces VCAM-1 expression (107). Blockade of CD80 expression has been shown to prevent clinical relapses and chronicity of experimental allergic encephalomyelitis (108-110); antibody blockade of CD40:CD40L interactions completely blocks T cell contact-induction of CD80 expression (25). Since neither IL-10 nor TGF-beta appear to down-regulate CD80 expression (52,53), the down-regulation of CD40L, and hence CD40L stimulation of CD80 expression, may therefore be a pivotal event in the shift from inflammatory to anti-inflammatory activities in the sclerotic lesion.

7. PERSPECTIVE.

The studies on experimenal allergic encephalomyelitis to date strongly support critical roles for CD40 and TNF-alpha (CD40-induced?) in the pathogenesis of sclerotic lesions and for TGF-beta in remission of the inflammatory episode. Although receptors other than CD40 (e.g., CD23 and CD69) have been shown to stimulate macrophage production of inflammatory cytokines *in vitro*, their role in the pathogenesis of inflammatory disease is still unexplored. The studies on T cell receptor transgenic and CD40L-deficient mice (105) indicate that CD40-independent receptor:ligand pairs and/or cytokines are sufficient to drive the development of disease once the T cells are activated. This is supported by the observation that administration of anti-CD40L antibodies after immunization with encephalitogenic peptide only partially interferes with the development

of disease. The identification of these CD40-independent receptors and of their role in the pathogenesis of inflammatory disease will be a major area of research interest throughout the next decade.

8. ACKNOWLEDGMENTS

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