Interleukin 1 or Tumor Necrosis Factor-α: Which Is the Real Target in Rheumatoid Arthritis?

JEAN-MICHEL DAYER

ABSTRACT. Much debate has focused on the relative importance of interleukin 1 (IL-1) and tumor necrosis factor-α (TNF-α) in the pathophysiology of rheumatoid arthritis (RA). The production of these cytokines by synovial macrophages is tightly regulated by cell–cell contact with T cells. During this contact, several surface molecules are implicated in contact mediated cytokine production, including CD40 ligand, CD11b/c, and CD69. Apolipoprotein A-I, an acute phase reactant (APR) that declines during systemic inflammation (reverse APR), inhibits cytokine production by interfering in the T cell–monocyte interaction. Although the effects of IL-1 and TNF-α overlap, they have somewhat differing roles in RA on the basis of evidence from several animal models. TNF-α appears to play a more important role in triggering events leading to inflammation both locally and systemically, whereas IL-1 is more involved at the local level in processes leading to cartilage and bone destruction and in impeding cartilage repair. However, IL-1 and TNF-α strongly synergize in numerous biological functions, both *in vitro* and *in vivo*. Blockade of IL-1 and TNF-α simultaneously provides favorable effects in collagen and adjuvant induced arthritis, illustrating the importance of both cytokines. (J Rheumatol 2002;29 Suppl 65:10–15)

Key Indexing Terms:
APOLIPOPROTEIN A-I | CD40 | CELL-CELL INTERACTIONS
RHEUMATOID ARTHRITIS | INTERLEUKIN 1 | TUMOR NECROSIS FACTOR-α

The cytokines interleukin 1 (IL-1) and tumor necrosis factor-α (TNF-α) are thought to contribute significantly to the pathophysiology of rheumatoid arthritis (RA)[1-3]. Macrophages are the primary source of these proinflammatory cytokines in the rheumatoid joint, but the major trigger leading to their production, at least in humans, remains unclear. Direct contact with activated T cells, possibly carrying a memory phenotype and no longer antigen dependent, may be an important pathway for inducing cytokine production by synovial macrophages. In addition, immune complexes, degraded products of the extracellular matrix, or other soluble factors present in the synovial fluid may trigger cytokine production.

The etiological event that leads to the onset of RA remains unknown. Conceptually, a danger signal or stress may promote acute inflammation that, in the appropriate environment, may allow transformed or denatured intrinsic body components to be presented as antigens to the immune system. As a result, dendritic cells, T cells, and macrophages interact, leading to a new pattern of cytokine production. The normal balance between proinflammatory and antiinflammatory cytokines may be disrupted, thereby allowing the proinflammatory mediators to predominate. It is important to realize, however, that individual cytokines may play differing roles under acute versus chronic inflammatory conditions. Thus, transforming growth factor-ß promotes acute inflammation by stimulating neutrophil chemotaxis, but it provides immunosuppressive actions during chronic inflammation. Similarly, IL-18 induces interferon-γ (IFN-γ) expression during acute inflammation, but it inhibits osteoclast differentiation during the chronic phase. These differences may explain why some investigators arrive at divergent results depending on the experimental model being used.

ROLES OF IL-1 AND TNF-α IN ARTHRITIS

The relative roles of IL-1 and TNF-α in RA have been the subject of much debate. TNF-α appears to have greater proinflammatory activity systemically than IL-1. In early studies, for example, injection of TNF-α produced high rates of mortality in animals, whereas IL-1 induced lethality was seen only at very high doses. In arthritis, these cytokines share many overlapping activities, but the pattern of their effects appears to differ somewhat on the basis of studies in experimental models, such as collagen induced arthritis, immune complex induced arthritis, and streptococcal cell wall arthritis[4-7]. TNF-α appears to play a more important role than IL-1 in causing local joint inflammation, whereas IL-1 appears to be more important than TNF-α in promoting cartilage and bone destruction. IL-1 also appears to block repair processes in cartilage to a greater extent than TNF-α. Both cytokines induce the expression of one

From the Division of Immunology and Allergy, Geneva University Hospital, Geneva, Switzerland.

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J-M. Dayer, MD.

Address reprint requests to Dr. J-M. Dayer, University Hospital, Immunology/Allergy Division, 1211 Geneva 14, Switzerland.
E-mail: jean-michel.dayer@hcuge.ch

another, although it remains controversial whether one is more potent than the other in this regard.

The activity of IL-1 and TNF-α is normally balanced by several endogenous inhibitors: IL-1 receptor antagonist (IL-1ra), soluble type II IL-1 receptor (sIL-1RII), and soluble TNF receptors (sTNF-R). In addition, about 20% of healthy individuals have autoantibodies to IL-1α, and in about 20% of them, the autoantibodies block the actions of IL-1. In one study, the presence of neutralizing autoantibodies to IL-1α was associated with a better prognosis in patients with chronic polyarthritis[8]. However, in a more recent study, the presence of anti-IL-1α autoantibodies in early RA did not correlate with clinical improvement or radiographic progression during 2 year followup[9].

IL-1ra, like IL-1α and IL-1ß, is a member of the IL-1 family[10]. Each member binds to the type I IL-1 receptor (IL-1RI). IL-1α and IL-1ß binding leads to intracellular signaling and biological effects, but IL-1ra binding does not transduce an intracellular signal. Contrary to IL-1α and ß, IL-1ra does not induce the formation of a heterodimer between IL-1RI and the accessory chain of the receptor. Therefore, IL-1ra functions as a natural antagonist that blocks access of IL-1α and IL-1ß to the receptor. For example, in organ cultures of fetal rat long bones and neonatal mouse calvariae, IL-1ra selectively blocked bone resorption induced by IL-1 but not by parathyroid hormone[11]. IL-1α and IL-1ß also bind to a second (type II) IL-1 receptor (IL-1RII), but this receptor acts as a "decoy" and does not transduce an intracellular signal. Both receptors can be cleaved and circulate as soluble proteins (sIL-1RI and sIL-1RII). The sIL-1RI is still capable of binding to IL-1ra, which reduces the amount of IL-Ra available to block the cell surface interactions between IL-1α and IL-1ß and the receptors[12]. In contrast, the sIL-1RII preferentially binds to the agonists IL-1α and IL-1ß. Accordingly, the best ways for blocking IL-1 are through using a combination of IL-1ra and sIL-1RII.

The importance of IL-1ra is illustrated by studies in IL-1ra deficient mice. Mice with a Balb/cA genetic background, but not those with a C57BL/6J background, spontaneously developed a chronic inflammatory polyarthropathy that resembled RA[13]. Histologically, marked synovial and periarticular inflammation were seen with articular erosion caused by invasion of pannus-like granulation tissue. The synovial space contained large numbers of inflammatory cells, principally neutrophils and lymphocytes, with fibrin clots also being evident. Other features included marked proliferation of synovial lining cells and osteoclast activation and resorption of bone matrix. In another study, IL-1ra deficient mice with another genetic background developed arterial inflammation as the prominent feature, suggesting that extraarticular manifestations may depend on the genetic background[14].

IL-1ra also blocks the deleterious effects of IL-1 on cartilage degradation and repair. IL-1 causes cartilage damage by stimulating the release of matrix metalloproteinases (MMP) and other proteolytic enzymes that degrade proteoglycans and type II collagen[15]. Perhaps of greater importance, IL-1 inhibits mechanisms of cartilage repair by reducing proteoglycan synthesis and by promoting chondrocyte apoptosis. In organ cultures of human cartilage, IL-1 inhibited production of sulfated glycosaminoglycans in a concentration dependent manner[16]. IL-1ß was about 6 times more potent than IL-1α in blocking this mechanism of cartilage repair; in turn, both were much more active than TNF-α. The reduction in glycosaminoglycan synthesis caused by IL-1ß was reversed competitively by addition of IL-1ra[17]. The importance of IL-1 in cartilage damage is illustrated in the chronic relapsing streptococcal cell wall arthritis model in mice. Relative to control wild-type animals, much less cartilage depletion was observed in IL-1ß deficient mice[7].

INTERACTIONS BETWEEN T CELLS AND MACROPHAGES

Immunohistochemical staining shows that both macrophages and T cells are present in rheumatoid synovial tissue[18]. More than 95% of the T cells found in rheumatoid synovium have the Th1 phenotype, and they express the chemokine CCR5 receptor. Direct contact between T cells and macrophages provides a signal for generation of IL-1 and TNF-α, which may be important in the proximal events associated with acute inflammation, as well as the more distal events leading to cartilage and bone destruction.

The production of IL-1 and TNF-α following T cell contact with macrophages was explored using a double chamber system, in which the upper and lower compartments were separated by a membrane[18]. The T cells and macrophages were incubated alone, in separate compartments on opposite sides of the membrane, and together in the same compartment. Phytohemagglutinin induced IL-1 and TNF-α production was greatly enhanced when T cells were cultured with macrophages in the same compartment (Figure 1). In contrast, lower levels of TNF-α and only small amounts of IL-1 were produced when T cells and macrophages were cultured in separate compartments, or when T cells were evaluated in the absence of any macrophages[19-21].

The type of cytokines produced by cell contact was largely dependent on the T cell phenotype, CD4+. T cell clones were generated that were specific for a purified protein derivative of *Mycobacterium tuberculosis* (Th1) or tetanus toxoid (Th2)[22]. The Th1 clone expressed the CCR5 chemokine receptor as a marker; it produced high levels of IFN-γ and low levels of IL-4. Conversely, the Th2 clone produced high levels of IL-4 and low levels of IFN-γ. Incubation of cell membranes from these antigen stimulated Th clones with the monocytic THP-1 cell line led to dose dependent cytokine production. Notably, the Th1 cell

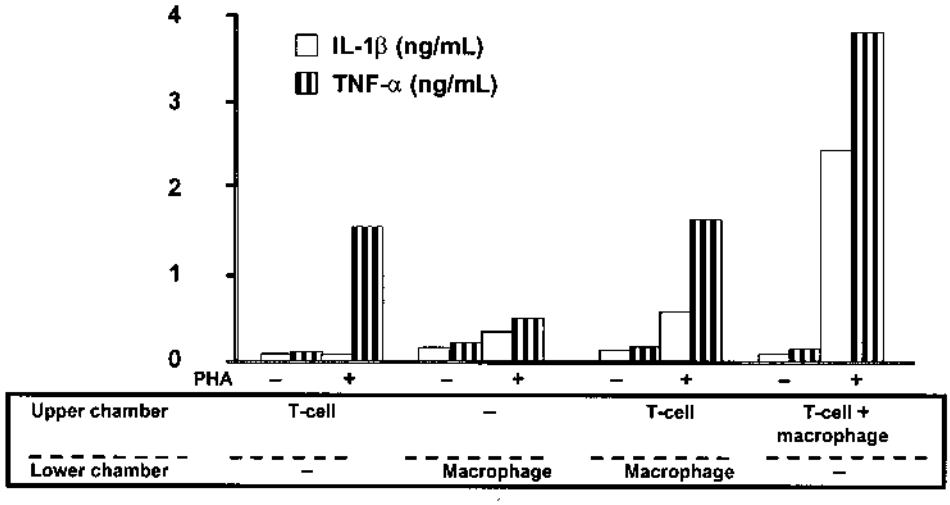

Figure 1. Role of cell–cell contact in the production of IL-1ß and TNF-α by macrophages. T cells and macrophages were cultured alone or together in a 2 chamber system, in which the upper and lower chambers were separated by a membrane. From Dayer and Burger, 1995[19], with permission.

membranes induced much higher levels of IL-1ß than did the Th2 membranes, whereas the Th2 membranes stimulated much greater IL-1ra production. These results suggest that Th1 and Th2 cells express unique cell surface molecules that can induce distinct proinflammatory or antiinflammatory responses by monocytes. In coculture experiments, addition of IL-2 — and even more so of IL-15 — induced an additional strong increase in the production of IL-1[23].

The identity of the corresponding surface molecules on T cells and macrophages that provide signals for IL-1 and TNF-α production are under investigation (Figure 2). An interaction between CD40 ligand (CD40L) on Th1 cells and CD40 on monocytes may be required. In coculture experiments, blocking the CD40L–CD40 interaction with a fusion protein or monoclonal antibody inhibited contact dependent IL-1ß and TNF-α production, but IL-1ra production was unaffected[23]. This observation supports the differential regulation of IL-1ß and IL-1ra by cell–cell interactions. However, the Th1 and Th2 clones expressed similar levels of CD40L, suggesting that other molecules preferentially expressed on the surface of Th1 cells must also be involved in the regulation of contact dependent cytokine production. Monoclonal antibodies to CD69 as well as CD11b and CD11c (but to a lesser extent CD11a) also block interactions between T cells and monocytes, and these cause 30% to 40% reductions in contact dependent IL-1ß and TNF-α production[24].

Adult human serum and, to a much lesser extent, human

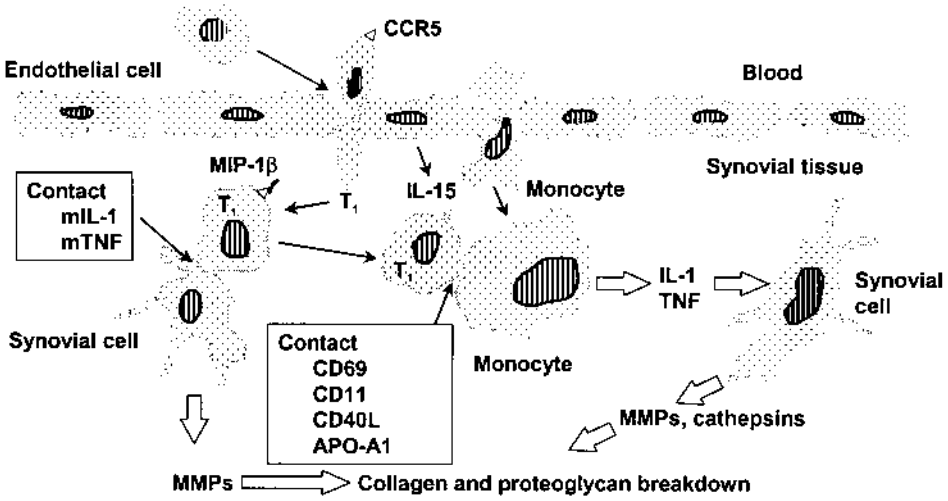

Figure 2. Scheme showing the effect of contact between T cells and either monocytes or synovial cells. CCR5: family chemokine receptor 5; APO-A1: apolipoprotein A1; MIP-1ß: macrophage inflammatory protein-1ß; mIL-1: membrane-bound IL-1; mTNF: membrane-bound TNF.

cord blood serum, but not fetal calf serum, inhibit IL-1ß and TNF-α production resulting from interactions between stimulated T cells and monocytes[25]. The factor in human serum that blocked contact dependent cytokine production was purified after sequencing and identified as apolipoprotein A-I (apo A-I), the major protein contained in high density lipoprotein (HDL). Apo A-I associated with HDL binds to stimulated T cells, thereby preventing contact mediated activation of monocytes and subsequent IL-1ß and TNF-α production. It is well established that IL-1, TNF-α, and IL-6 stimulate the release of acute phase reactants from hepatocytes, including C-reactive protein, complement C3, and fibrinogen (Figure 3). Simultaneously, several hepatocyte derived proteins also decrease during systemic inflammation, one of which is apo A-I. One could speculate that the decrease in apo A-I during the inflammatory process may aggravate the clinical situation by allowing greater contact between T cells and monocytes, thereby resulting in higher levels of IL-1 and TNF-α production.

T cells also interact with synoviocytes to induce production of MMP and prostaglandin (PG) E_2 (Figure 2)[26]. Notably, the production of MMP-1 by contact between stimulated T cells and synoviocytes was greater than that induced by optimal concentrations of IL-1ß, whereas cell contact and IL-1ß stimulated similar PGE_2 production. Production of tissue inhibitor of metalloproteinase-1 was also increased by cell contact but only during the first 2–4 hours of coculture. According to studies with monoclonal antibodies and cytokine antagonists, the cell associated molecules involved in contact dependent MMP-1 and PGE_2 production by synoviocytes were IL-1α and TNF-α. CD40L, CD11b, and CD69 are not involved in the interaction between T cells and synoviocytes, contrasting with their role in T cell–monocyte contact.

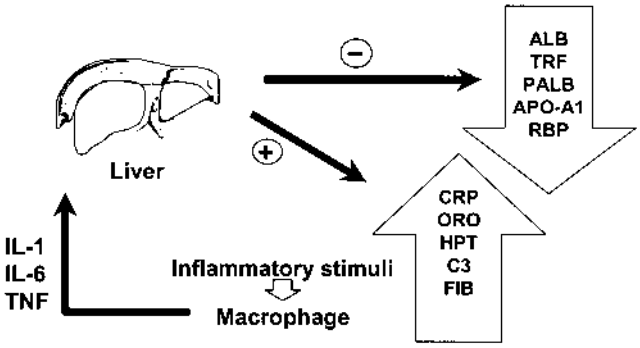

Figure 3. Regulation of acute phase proteins by inflammatory mediators. The production of apo A-I declines during systemic inflammation.

SYNERGISM BETWEEN IL-1 AND TNF-α

The relative amounts of IL-1 and TNF-α may depend on the nature of the stimulus and the stage of disease. Nevertheless, the ability of these cytokines to cause overlapping effects raises the possibility that they may act synergistically to promote pain and inflammation, cause matrix degradation, and limit cartilage repair (Figure 4). In each of these aspects, one of the cytokines may have a greater effect than the other. For example, TNF-α may be more important in upregulating chemokine and cell adhesion molecule expression, which is required for inflammatory cell infiltration into the rheumatoid joint. Conversely, IL-1 may be more important

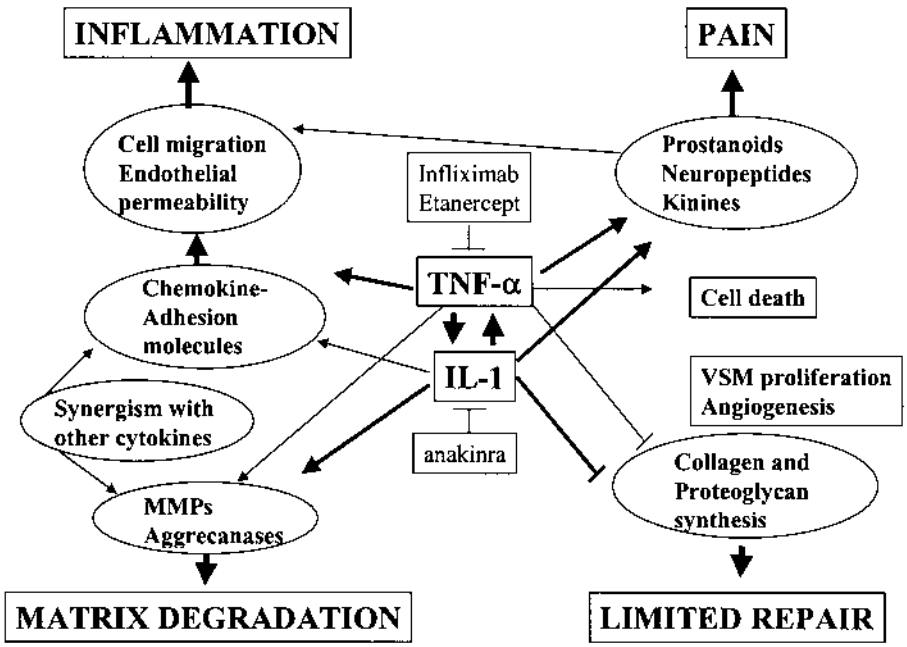

Figure 4. Central role of IL-1 and TNF-α in the pathogenesis of RA. Adapted from Bresnihan and Dayer[28], with permission.

in stimulating MMP and other enzymes that degrade cartilage, and it may also be the predominant cytokine that limits cartilage repair. By combining agents that block these cytokines, it may be possible to control most mechanisms involved in RA pathogenesis. However, it is also believed that in RA the resorption of the subchondral bone, and to a lesser extent the cartilage, may occur not only from the synovial site but also from the bone marrow. It follows that osteoclasts play a crucial part.

The beneficial effects of blocking IL-1 and TNF-α simultaneously have been well established for collagen induced arthritis and in adjuvant induced arthritis models in rats[27]. In collagen induced arthritis, animals were treated with recombinant human IL-1ra (3 mg/kg) and PEGylated sTNF-RI (100 mg/kg) either alone or in combination. The presence of inflammation, pannus, cartilage damage, and bone resorption in ankle joints was scored histopathologically on a scale of 0–4. Treatment with either IL-1ra or PEGylated sTNF-RI alone partially reduced each histologic variable. However, when administered concomitantly, additive effects on inflammation were seen, but much greater than additive effects were achieved for the other 3 variables. Similarly, in the adjuvant arthritis model, ankle swelling was reduced in a more than additive manner by the combination of IL-1ra and PEGylated sTNF-RI. It remains to be determined whether simultaneously blocking both IL-1 and TNF-α in patients with active RA will be more effective than current combination regimens involving either IL-1ra or a TNF-α blocker in combination with methotrexate.

SUMMARY

Both IL-1 and TNF-α are important in the pathogenesis of RA, and interactions between the 2 may produce synergistic effects. Contact between cells present in the rheumatoid synovium, notably T cells and macrophages, may be an important trigger for production of these cytokines. Some experimental evidence suggests that TNF-α may be more important in promoting mechanisms leading to inflammation, whereas IL-1 may be more important in processes leading to cartilage and bone destruction and in limiting mechanisms involved in cartilage repair. However, the relative importance of these cytokines in patients with active RA may differ somewhat from evidence collected in experimental models. Nevertheless, the ability of biologic therapy directed against either IL-1 or TNF-α to reduce clinical signs and symptoms of disease and slow radiographic progression argues that both cytokines are indeed important, at least in individual patients.

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