

## Supplement Review

# Cytokine regulation in RA synovial tissue: role of T cell/macrophage contact-dependent interactions

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## Chapter summary

Several groups have documented the expression of cytokines in rheumatoid arthritis synovial tissue over the past 15 years or so. These studies have indicated that most cytokines examined are expressed at the mRNA levels at least, and many other cytokines are found in abundance as proteins. Our attention has recently focused on the mechanisms that induce and regulate tumour necrosis factor and IL-10. Other workers and ourselves have found that cell-cell contact is an important signal for the induction of cytokines, and our work has demonstrated that tumour necrosis factor and IL-10 production in rheumatoid arthritis synovial joint cells cultures is dependent on T cell/macrophage interaction. In this chapter, we review recent advances in this area and also highlight areas where new therapeutic intervention opportunities arise.

**Keywords:** cognate, differentiation, macrophage, signalling, T cells

## Historical background

It is now well accepted that the spontaneous production of proinflammatory cytokines (in particular, tumour necrosis factor [TNF] and IL-1) produced locally in the inflamed synovial joint contribute directly/indirectly to the pathogenesis of rheumatoid arthritis (RA) [1]. These observations have arisen from *ex vivo* studies on human synovial cultures, immunohistochemical and mRNA analysis of synovium, and *in vivo* studies in animal models of arthritis.

These investigations led to the development of several TNF and IL-1 inhibitors, two of which are currently licensed Remicade (chimeric anti-TNF antibody) and Enbrel (TNF-receptor fusion protein). While such therapies targeting TNF in chronic inflammatory disease are very successful [2], it is also apparent that long-term blockade of a cytokine such as TNF, which is important in

innate and acquired immunity, may lead to an increase in latent and/or opportunistic infections. This is now apparent, with a small but significant increase in unusual infections, as well as the re-emergence of latent tuberculosis, particularly in Central and Eastern Europe [3].

There is thus a need to understand what mechanisms lead to the production of proinflammatory cytokines in RA synovial tissue, and further to determine how this is linked to homeostatic regulation. It has been observed that while the production of proinflammatory cytokines and enzymes is increased in RA, this is offset to some degree by the action of the endogenous anti-inflammatory cytokines and cytokine inhibitors. Of particular importance in this respect is IL-10, an important regulator of TNF- $\alpha$  and IL-1 $\beta$  spontaneously produced by macrophages in the rheumatoid joint [4,5]. Thus, if endogenous IL-10 is blocked in RA synovial

cell cultures, the spontaneous production of both TNF and IL-1 increases significantly [4]. There is therefore an important need to develop therapies that block proinflammatory pathways but leave unaffected those pathways that regulate immunoregulatory cytokines such as IL-10.

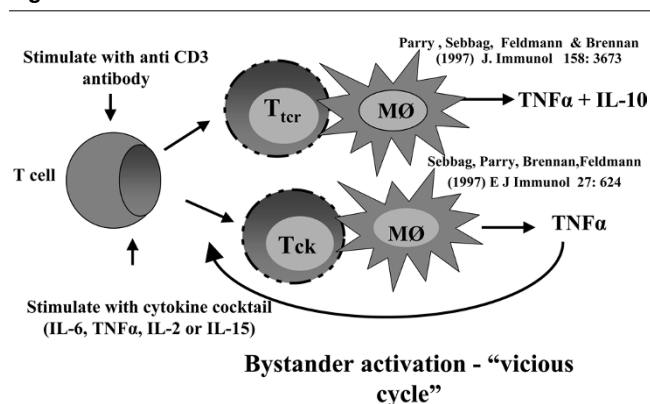
### Cognate-dependent interactions

Histological studies of synovium in RA have indicated that this tissue is very cellular, and that several different cell types including macrophages and T cells are in close proximity [6]. This may suggest that contact signals between macrophages and T cells could be of importance *in vivo* in modulating macrophage function. We have found that TNF- $\alpha$  production in RA synovium is T-cell dependent, as removal of CD3-positive T cells from RA synovial mononuclear cells resulted in significant reduced macrophage TNF- $\alpha$  production [7]. Furthermore, this signal was abrogated if physical contact between the two cell types was blocked.

Direct-contact-mediated interactions have been studied by several groups using transformed T-cell lines and monocytic lines, and have been found to play a role in inducing the synthesis of several cytokines including IL-1 $\beta$ , TNF- $\alpha$ , IL-10 and metalloproteinases [8–12]. We have studied T cell/monocyte cognate interactions using cells isolated from the peripheral blood of normal donors. Importantly, we observed that the manner in which T cells were activated influenced the profile of cytokines induced in the monocytes. Thus, if blood T cells were activated with cross-linked anti-CD3, this induced the production of TNF- $\alpha$  and IL-10 in monocytes [12]. However, if the T cells were stimulated with a cocktail of cytokines (TNF- $\alpha$ , IL-2 and IL-6) for 8 days (bystander activation), TNF- $\alpha$  production followed but IL-10 production did not [11]. These observations suggested to us that cytokine-stimulated T cells (Tck) may be the actual T cells in RA synovial tissue that induce macrophage TNF- $\alpha$  production, because they induce an unbalanced, proinflammatory cytokine response from monocytes and they could be part of a vicious cycle (Fig. 1). Indeed, in addition to the mechanism of T-cell activation determining the cytokine profile produced by monocytic cells, the corresponding T-cell phenotype would also appear to be important, as one study [13] suggested a differential regulation of monocyte-derived cytokine production by Th1-like and Th2-like cells. This study describes CD4<sup>+</sup> Th1 clones inducing high levels of IL-1 $\beta$  production by THP-1 monocytes, whereas Th2 clones induced higher levels of IL-1ra. This implies that Th1 cells are proinflammatory whereas Th2 cells are anti-inflammatory.

The hypothesis that RA T cells mimic the action of Tck cells is attractive since T cells found in RA synovium have unusual characteristics. The T cells are relatively small and noncycling, but have features of activation, with over one-

Figure 1



Cytokine disequilibrium induced by cytokine-stimulated T cells (Tck). M $\phi$ , monocytes; T<sub>ter</sub>, T-cell-receptor-dependent stimulated T cells.

half expressing HLA class II, VLA antigens, CD25 and CD69 [14,15]. T-cell receptor analysis has not revealed a consistent pattern, and responses to putative autoantigens have not been easy to reproduce (reviewed in [16]). Based on these features and the low capacity of T cells to produce T-cell-derived cytokines, it has been proposed that T cells in the joint may not be involved in the later stages of the disease [17]. We have, however, proposed that they are involved in disease pathology through the activation of macrophages to induce TNF. The environment of the RA synovium is favourable to Tck cells, as it is rich in cytokines. Unutmaz *et al.* described bystander-activated T cells generated from normal peripheral blood mononuclear cells (PBMC) with IL-2, IL-6 and TNF- $\alpha$  [18]. We found that IL-15 could, by itself, mimic the IL-6/TNF- $\alpha$ /IL-2 cocktail used to activate Tck [11]. IL-15 is of particular interest as it is found in RA synovium [19] and can activate peripheral blood T cells to induce TNF- $\alpha$  synthesis in U937 cells or in adherent RA synovial cells in a contact-dependent manner [20,21]

Other cognate cell-to-cell interactions occur in the synovial joint, which contribute to the disease pathology observed in RA. These interactions include endothelial cell/T cell and fibroblast/T cell interactions. During the early stages of inflammation there is a large cellular infiltration from the peripheral circulation to the synovial joint, where interactions between T cells and vascular endothelium drive further extravasation and infiltration by the expression of cell adhesion molecules, chemokines and cytokines [22–25]. In addition, the earliest infiltrating cells, neutrophils, can be activated by contact-mediated interaction with T cells, as determined by the ability of these neutrophils to be primed for respiratory burst by formyl-methionine leucine phenylalanine peptide [26].

As the pathology of RA progresses to chronic inflammation and pannus forms at the cartilage-pannus junction,

the interactions between T cells and fibroblasts/macrophages predominate. The interaction between stimulated T cells and dermal fibroblasts or synoviocytes has recently been shown to induce MMP-1 (collagenase) and TIMP-1, with an imbalance in favour of the proinflammatory MMP-1 [27], also inhibiting the synthesis of type I and type III collagen by fibroblast cells [28].

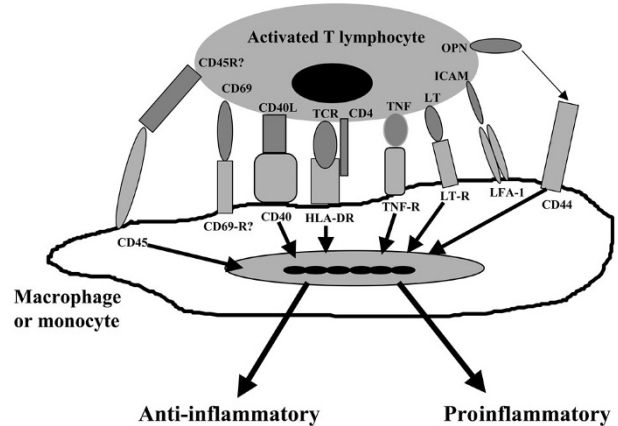
Studies undertaken thus far have documented the potent stimulatory activity of T cells on monocyte cytokine production during the pathology of RA. The abundance of T cells and monocytes in the peripheral circulation, which have the potential to physically interact with each other, however, does not seem to induce cytokine production. This led to the hypothesis and subsequent characterisation of an inhibitory factor, apolipoprotein A-1, preventing monocyte activation in the plasma/serum [29]. The presence of apolipoprotein A-1 and subsequent inhibition of T-cell-mediated macrophage activation may suggest this molecule to have a useful anti-inflammatory therapeutic effect in chronic inflammatory diseases such as RA.

### Cell surface molecules

As contact-dependent signals have been demonstrated to be of importance, much attention has focused on the probable candidate molecules on the surface of cells mediating these functions. Specific surface interaction molecules that have been reported to mediate induction of monocyte cytokine synthesis include CD69, LFA-1 [8,30], CD44 [31], CD45 [32], CD40 [33], membrane TNF [12], and signalling lymphocytic activation molecule [34]. Our studies further demonstrated that T cells activated through the T-cell receptor complex induced monocyte IL-10 synthesis, which was partially dependent on endogenous TNF- $\alpha$  and IL-1, and that T-cell membrane TNF- $\alpha$  was an important contact-mediated signal [12,35]. However, IL-10 synthesis still occurred when TNF- $\alpha$  and IL-1 were neutralised, suggesting that there are other TNF/IL-1-independent signals required for IL-10 synthesis.

While TNF clearly plays a role in IL-10 production, there are other signals independent of TNF and IL-1 that may be involved. Of particular interest are members of the TNF/TNF-receptor family, which include CD40, CD27, CD30, OX-40 and LT $\beta$ . The ligands of these TNF-receptor molecules have been described as upregulated on T-cell activation. In addition, CD40L, 4-1BB, CD27L and CD30 have been described to be released as soluble molecules after activation [36–39]. The interaction between CD40L and CD40 has been suggested to be important for inducing both IL-1 and IL-12 synthesis following T-cell interaction with monocytes [33,40] and, more recently, to mediate IL-10 production by human microglial cells on interaction with anti-CD3-stimulated T cells [41]. In addition, we have recently shown that CD40L/CD40 interaction mediates cognate induction of macrophage IL-10

**Figure 2**



Potential ligand/counter ligand interactions involved in cytokine production by macrophages. HLA-DR, human leukocyte antigen – class II, subtype DR; ICAM, intracellular adhesion molecule; LT, lymphotoxin; MMP, matrix metalloproteinase; OPN, osteoprotegrin; RNI, reactive nitrogen intermediates; TCR, T-cell receptor; TNF, tumour necrosis factor.

[42]. The potential involvement of these ligand/counter ligand pairs on cells interacting in synovial membrane tissue is represented in Figure 2.

### Differentiation status

In addition to the stimulus encountered by the T cells, our data has indicated the importance of the differentiation state of the monocyte in determining cytokine profiles in response to activated T cells. We observed that CD40 signalling augmented lipopolysaccharide (LPS)-induced IL-10 production by monocytes, but also observed that CD40 ligation induced IL-10 production by differentiated monocytes (macrophages) in the absence of LPS. Indeed, the priming mechanism of the macrophage determined the cytokine profile: macrophage-colony-stimulating factor preprogrammed macrophages to produce both IL-10 and TNF- $\alpha$  on stimulation by CD40L or Tck, whereas IFN- $\gamma$  priming resulted predominantly in TNF- $\alpha$  [42].

IFN- $\gamma$ -primed macrophages, however, can produce an endogenous IL-10 activity that is not secreted into the supernatant on cell contact with either Tck or CD40L transfectants, as neutralisation of endogenous IL-10 resulted in a marked increase in TNF- $\alpha$  production. This observation may agree with the report of membrane-associated IL-10 [43] and may highlight differences in the ability of these two types of macrophage-like cells to process cytokines.

Macrophage-colony-stimulating factor can usually be readily detected in the RA joint, while IFN- $\gamma$  is scarce (reviewed in [44]). This may indicate why both TNF- $\alpha$  and

IL-10 are found in synovial membrane cell cultures. This preprogramming of macrophages would appear to be irrespective of the triggering stimulus because macrophages stimulated by either Tck, CD40 ligation or LPS result in similar cytokine profiles. It would thus appear that the route of differentiation of the monocyte is critical in the induction of IL-10 in cognate interactions between activated T cells and macrophages.

### Signalling pathways

TNF- $\alpha$  synthesis in monocytes in response to some stimuli (LPS) but not others (zymosan or CD45 ligation) is NF- $\kappa$ B dependent [32,45,46]. It is thus of interest to observe that Tck-induced, but not T-cell-receptor-dependent stimulated T cell (Tcr)-induced, TNF- $\alpha$  production in monocytes is NF- $\kappa$ B dependent. Furthermore, whereas phosphatidylinositol 3-kinase (PI3K) inhibitors blocked Tcr induction of TNF- $\alpha$ , they paradoxically augmented TNF- $\alpha$  in monocytes stimulated by Tck cells. Importantly, we then found that RA T cells behaved like Tck cells, in that the induction of TNF- $\alpha$  in resting peripheral blood monocytes was NF- $\kappa$ B dependent but superinduced if PI3K was blocked. An identical result was observed if NF- $\kappa$ B or PI3K was blocked in the RA synovial cell cultures.

IL-10 production in monocytes/macrophages is equally complex. In response to LPS, IL-10 production is dependent on endogenous IL-1 and TNF- $\alpha$ . Furthermore, there is selective mitogen-activated protein kinase (MAPK) utilisation where IL-10 production was dependent on p38 MAPK, and TNF- $\alpha$  production was dependent on both p38 MAPK and p42/44 MAPK [47]. The involvement of p38 MAPK activity in IL-10 production subsequently led to the characterisation of the downstream effector, hsp27, as an anti-inflammatory mediator [48].

Little is known, however, regarding the involvement of the PI3K pathway in macrophage production of IL-10. PI3K and its downstream substrate p70S6K mediate IL-10-induced proliferative responses but not anti-inflammatory effects [49]. A recent study from our laboratory has described Tck-induced macrophage IL-10 production to be dependent on PI3K and p70S6K, whereas TNF- $\alpha$  production is negatively regulated by PI3K and is p70S6K dependent [50]. This suggests that IL-10 and TNF- $\alpha$  share a common component, p70S6K, but differentially utilise PI3K activity. These results are reproduced in the spontaneous cytokine production by RA synovial mononuclear cells (RA-SMCs) and by cocultures of RA synovial T cells with macrophages (RA-T/macrophage cocultures), further suggesting the relevance of this Tck/macrophage cognate coculture system as a model for cytokine production occurring in the inflamed synovium of the rheumatoid joint.

Although many other studies have implicated other signalling cascades in the induction of IL-10 production, not

much work exists on the signalling required in macrophages stimulated by cognate interactions with fixed activated T cells. PKC and cAMP signalling have been implicated in IL-10 and TNF- $\alpha$  production and are currently under investigation in our group. Preliminary results would suggest that both these cascades differentially regulate IL-10 and TNF- $\alpha$ .

Studies undertaken by other groups have reported the involvement of the cAMP/PKA pathway in the induction of IL-10 production by human PBMC. The membrane-permeable dibutyl cAMP was capable of elevating IL-10 mRNA and of augmenting LPS-induced IL-10 production, but on its own was incapable of producing IL-10 protein [51]. This work also demonstrated a role for PKC in the induction of IL-10 by LPS using the PKC inhibitors, calphostin C and H-7. This result contradicts our data but may reflect that this study used PBMC, a heterogeneous population, as compared with purified monocyte-derived macrophages.

In addition, the selective inhibition of phosphodiesterase type IV by rolipram was found to augment LPS-induced IL-10 production by murine peritoneal macrophages. The mechanism of this was thought to be as a consequence of LPS inducing the anti-inflammatory mediator, prostaglandin E<sub>2</sub>, which in turn upregulates intracellular cAMP via stimulation of adenylate cyclase activity [52].

### Concluding remarks

The cognate activation of macrophages by T cells has focused almost exclusively on the membrane interactions mediating the macrophage effector function, such as nitric oxide release, phagocytosis, B-cell help and, more recently, the cytokine profiles induced. The control of T-cell-induced IL-10 and TNF- $\alpha$  production by monocyte-derived macrophages is complex and is regulated at many levels. These levels include priming of the monocyte/macrophage, T-cell stimulation, and hence specific ligand/receptor interaction, and the resulting signal cascades and crosstalk between them. The continued study of these contact-mediated interactions, the signal transduction distal to the receptor and how they compare between the induction of IL-10 and TNF- $\alpha$  may discover potential therapeutic targets selectively affecting proinflammatory TNF- $\alpha$  production without affecting anti-inflammatory IL-10 production. Such targets will prove to be of great benefit in the treatment of such chronic inflammatory diseases as RA.

### Glossary of terms

MAPK = mitogen-activated protein kinase; PI3K = phosphatidylinositol 3-kinase; Tck = cytokine-stimulated T cells; Tcr = T-cell-receptor-dependent stimulated T cells.

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