

Review

Cytokines in chronic rheumatic diseases: is everything lack of homeostatic balance?Carlo Chizzolini¹, Jean-Michel Dayer² and Pierre Miossec³¹Department of Immunology and Allergy, University Hospital and School of Medicine, Geneva University Hospital, 1211 Geneva 14, Switzerland²School of Medicine, University of Geneva, rue Michel Servet 1, 1211 Geneva 14, Switzerland³Department of Immunology and Rheumatology, Hospital Edouard Herriot, University of Lyon, 69437 Lyon, FranceCorresponding author: Carlo Chizzolini, carlo.chizzolini@unige.ch

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Arthritis Research & Therapy 2009, **11**:246 (doi:10.1186/ar2767)**Abstract**

Biological systems have powerful inbuilt mechanisms of control intended to maintain homeostasis. Cytokines are no exception to this rule, and imbalance in cytokine activities may lead to inflammation with subsequent tissue and organ damage, altered function, and death. Balance is achieved through multiple, not mutually exclusive, mechanisms including the simultaneous production of agonist and antagonistic cytokines, expression of soluble receptors or membrane-bound nonsignaling receptors, priming and/or reprogramming of signaling, and uncoupling of ligand/receptor pairing from signal transduction. Insight into cytokine balance is leading to novel therapeutic approaches particularly in autoimmune conditions, which are intimately linked to a dysregulated cytokine production.

Introduction

To explore the complex regulation of cytokine activities it may be of help to bear in mind the example of rheumatoid arthritis (RA). A major step forward in RA treatment was achieved when it became possible to control disease manifestations such as joint destruction by blocking TNF. This could indicate that a single cytokine, in this case TNF, drives unopposed a series of events that lead to inflammation and destruction. The situation is less simple inside the joint, however, where proinflammatory cytokines co-exist alongside their endogenous inhibitors. This is a consequence of ongoing processes in which proinflammatory stimuli induce their anti-inflammatory counterparts and the imbalance between the two results in disease.

The cytokine network is a homeostatic system that may be comparable with the acid/base equilibrium. The biological activity of any cytokine in biological fluids can be interpreted correctly only by taking into account the activities of other

synergistic or antagonistic cytokines, of their respective inhibitors, and the extent to which each cytokine receptor is expressed. Interactions between intracellular signals modulate further cytokine activities. In addition, cell types with polarized patterns of cytokine production contribute to the balance. Owing to their potent activities in many different processes – including cell growth and differentiation, organ development, inflammation, immune response, and repair processes aiming at homeostasis – cytokine activities have to be tightly controlled. Since one of the main functions of cytokines is to mediate interactions between the immune and inflammatory responses, it is thought that chronic immunoinflammatory diseases might be caused in part by the uncontrolled production of cytokines. Furthermore, depending on the stage of inflammation or the biological effect under scrutiny, the same cytokine may have proinflammatory or anti-inflammatory activities. Many different mechanisms of regulation have been identified affecting both cells and soluble mediators (Table 1).

The present review describes the key levels of imbalance that have been associated with chronic inflammation and tissue destruction. This has to be integrated in general processes of disease initiation through the innate and adaptive immune responses ending in tissue and organ damage (Figure 1).

Balance in cytokines**Balance between IL-1 and IL-1 natural antagonists**

Amongst the most powerful proinflammatory cytokines, IL-1 stands out as a paradigmatic example of fine-tuned regulation of biological activities through a complex system of ligands with agonist and antagonist functions, as well as signaling

CCR = CC-family chemokine receptor; DARC = Duffy antigen receptor for chemokines; EAE = experimental allergic encephalomyelitis; Foxp3 = forkhead box p3; IFN = interferon; IL = interleukin; IL-1R = IL-1 receptor; IL-6R α = IL-6 receptor alpha; IL-1Ra = IL-1 receptor antagonist; NF = nuclear factor; RA = rheumatoid arthritis; RANTES = regulated on activation, normal T-cell expressed and secreted; SIGIRR = single immunoglobulin IL-1-related receptor; sIL-6R α = soluble IL-6R α ; SOCS = suppressors of cytokine signaling; STAT = signal transducer and activator of transcription; TGF β = transforming growth factor beta; Th = T-helper type; TNF = tumor necrosis factor; Treg = T cell with regulatory function; Wnt = wingless integration site.

Table 1

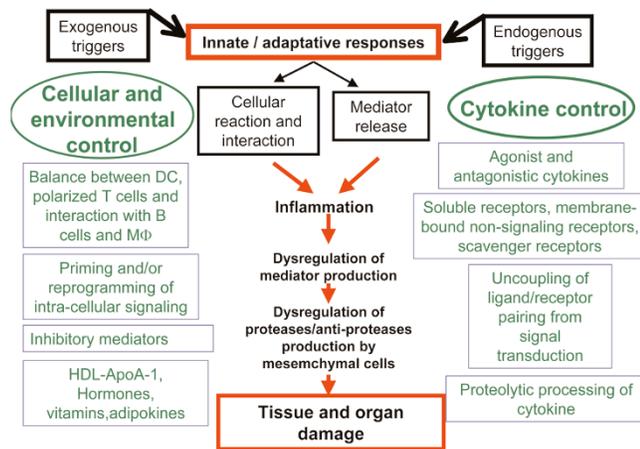
Balance in cytokine activities according to biological processes

Process	Cytokines
Inflammation	IL-1 / IL-1 receptor antagonist, IL-1 receptor II, soluble IL-1 receptor I, soluble IL-1 receptor II TNF / soluble TNF receptor I, soluble TNF receptor II IL-6 / soluble gp130 IL-18 / IL-18 binding protein IL-22 / IL-22 binding protein IL-13 / IL-13 receptor alpha CXCL ^{ELR+} / CXCL ^{ELR-} Several proinflammatory chemokines (CXC and CC) / Duffy antigen receptor for chemokines Several proinflammatory chemokines (CC not CXC) / D6 CCL19, CCL21, CCL25, CXCL13 / CCX-CKR Chemerin 9 / chemerin 15
Immune cell responses	Th1 cells / Th2 cells Th17 cells / Th2 cells Th17 cells / T cells with regulatory function T cells with regulatory function / Th1, Th2, Th17 cells
Tissue repair and remodeling	Transforming growth factor beta / TNF IL-1 / IFN γ IL-4 / IFN γ
CD4 T-cell differentiation	IL-12 / IL-4 Transforming growth factor beta / IL-6 + T-cell growth factor beta
Tissue destruction	Osteoprotegerin / RANKL WNT / Dickkopf-1
Metabolism	Adiponectin / leptin, vistatin, resistin

In view of the pleiotropic actions of cytokines, the table presents a far from complete view of possible opposing activities of cytokines and their ligands. The back slash (/) separates the opposing molecules in respect of a given biological activity. RANKL, receptor activator of NK κ B ligand; WNT, wingless integration site.

and non-signaling receptors (Figure 2). First of all, a natural ligand of IL-1 receptors – IL-1 receptor antagonist (IL-1Ra) – prevents recruitment of the accessory protein needed to signal, thus acting as a competitor to IL-1 [1]. Interestingly, IL-1Ra is preferentially produced by monocytes/macrophages stimulated by anti-inflammatory cytokines (see below). Second, two IL-1 receptors (IL-1RI and IL-1RII) are expressed at the surface of many cell types. An important functional difference, however, exists between the two receptors. Indeed, in contrast to IL-1RI, which transduces the signal, IL-1RII does not transduce and acts as a decoy receptor. Furthermore, both receptors may be shed from the cell surface by matrix metalloproteinases, and by binding to IL-1 or IL-1Ra soluble receptors may modulate their bioavailability, ultimately affecting cell responses. One of the many members of the IL-1 family, IL-1F5, also has inhibitory activities [2].

Some patients have autoantibodies to IL-1 α and these may also play a role by blocking IL-1 biological activity. Regulation is also provided by single immunoglobulin IL-1-related receptor (SIGIRR), also known as Toll-IL-1 receptor 8, which is a member of the Toll-like receptor/IL-1R family. Its small single extracellular immunoglobulin domain does not support ligand binding. Besides, the intracellular domain of SIGIRR cannot activate NF κ B because it lacks two essential amino acids (Ser447 and Tyr536) in its highly conserved Toll-IL-1 receptor domain. SIGIRR rather acts as an endogenous inhibitor of Toll-like receptor and IL-1 signaling, because overexpression of SIGIRR in Jurkat or HepG2 cells substantially reduced lipopolysaccharide-induced or IL-1-induced activation of NF κ B. Furthermore, lupus-prone mice have an accelerated course of disease when lacking Toll-IL-1 receptor 8 [3,4].

Figure 1

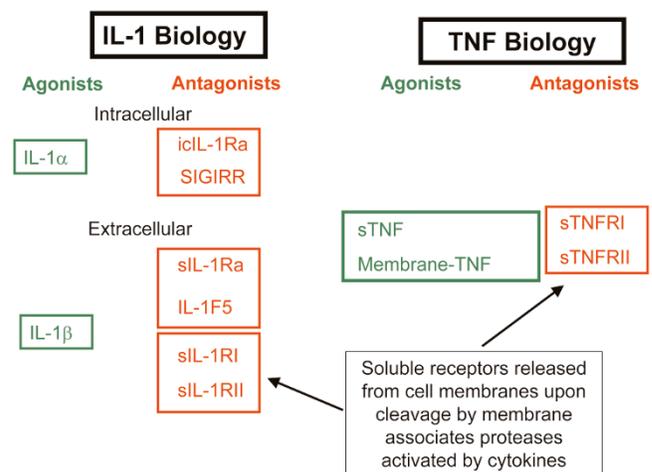
Conceptual framework for the role of cytokine imbalance in the pathogenesis of chronic inflammatory diseases. DC, dendritic cells; HDL-ApoA-1, high-density lipoprotein apolipoprotein A1; MΦ, macrophage.

The production by monocytes–macrophages of IL-1 and IL-1Ra is dependent on many distinct stimuli, including T-cell contact. Of interest, apolipoprotein A1, a negative acute-phase reactant, may act as negative feedback regulator by reducing IL-1 but not IL-1Ra production induced by T-cell contact. IFN β favors the production of IL-1Ra while simultaneously inhibiting IL-1. Similar activities are shared by IL-4, IL-13 and transforming growth factor beta (TGF β), which in this context are generally considered anti-inflammatory in that they increase IL-1Ra and, to a lesser extent, decrease IL-1 production (Table 2). A similar type of regulation is provided by leptin, which can modulate the expression of IL-1Ra and the release of IL-1 β by beta cells in human islets [5].

Phosphatidylinositol 3 kinase is among the most important signaling pathways involved in the control of the IL-1/IL-1Ra balance in human monocytes, in so far as inhibition of phosphatidylinositol 3 kinase delta markedly decreases IL-1 while increasing IL-1Ra [6,7]. A further example of the plasticity of the IL-1/IL-1Ra balance in human monocytes is the increase in IL-1Ra but decrease in T-cell-induced IL-1 β in the presence of glatiramer acetate, a therapeutic agent used in multiple sclerosis [8].

Balance in TNF and IL-6 activities

TNF and IL-6 have become successful targets of biological therapies in a variety of inflammatory conditions starting with RA, thus underling their pivotal role in inflammation. Several excellent reviews have been devoted to these two cytokines and their relevance in human diseases [9-13]. Therefore we shall here overview only the basic mechanisms involved in the regulation of their biological activities, in particular stressing differences in the activity of their respective soluble receptors.

Figure 2

Schematic representation of agonists and antagonists determining the biological activities of IL-1 and TNF. iCL-1Ra, intracellular IL-1 receptor antagonist; SIGIRR, single immunoglobulin IL-1-related receptor; sIL-1Ra, soluble IL-1 receptor antagonist; sIL-1R, soluble IL-1 receptor; sTNF, soluble TNF; sTNFR, soluble TNF receptor.

Trimeric TNF, mostly produced by activated macrophages and T cells, acts by binding to two distinct TNF receptors: TNF-RI (p55), which is widely expressed; and TNF-RII (p75), mostly present on cells of the immune system (Figure 2). Both receptors can be enzymatically shed from the surface of the cells and, once in the body fluids, both can bind TNF and neutralize its biological activity [14]. The receptors therefore act as natural inhibitors of TNF, and their production is regulated by several stimuli including TNF itself.

At variance with TNF, IL-6 acts by binding to a heterodimeric receptor composed of the common gp130 chain, shared with oncostatin M, IL-11, ciliary neurotrophic factor-1, cardiotropin-1, and leukemia inhibitor factor, and to its specific IL-6 receptor alpha (IL-6R α). The signaling chain is gp130, affinity of which for IL-6 is increased in the presence of IL-6R α . Of interest, IL-6R α exists as a cell-bound form expressed on few cell types – particularly hepatocytes, phagocytes, and some lymphocytes – but also in a soluble form abundantly present in body fluids. Soluble IL-6R α (sIL-6R α) has the capacity of binding to IL-6 and to increase its affinity for gp130. Since gp130 is ubiquitously expressed, sIL-6R α offers the opportunity to cells that do not express IL-6R α to become responsive to IL-6, a phenomenon called trans-signaling. In transgenic mice sIL-6R α functions as a carrier protein for its ligand, thereby markedly prolonging the plasma half-life of IL-6, indicating that IL-6 signaling is increased by sIL-6R α [15]. The agonistic properties of sIL-6R α by enhancing IL-6 signaling are well documented. There are results indicating also antagonistic properties of sIL-6R α , however, which may explain why IL-6 may in some circumstances acts as an anti-inflammatory mediator [16].

Table 2**Cytokine roles categorized according to their contribution to inflammation in rheumatoid arthritis**

Proinflammatory	Ambivalent	Anti-inflammatory
TNF	IFN γ	IL-1 receptor antagonist
IL-1	Transforming growth factor beta	IL-4 ^a
IL-12	IL-6 ^b	IL-13
IL-15		IL-10 ^c
IL-17A/IL-17F		IL-25
IL-18		IL-27
CXCL8		IL-35
CCL3		
CCL2		7ND

7ND, N-terminal natural deletion variant of monocytes chemotactic protein-1/CCL2. ^aIL-4 is anti-inflammatory in the context of rheumatoid arthritis synovial inflammation. By impacting on IgE production, however, IL-4 is a key cytokine in IgE-mediated inflammation. Similar considerations apply to IL-13. ^bIL-6 may be proinflammatory or anti-inflammatory according to the circumstances. IL-6 blockade has been shown to be clinically useful to control rheumatoid arthritis in randomized trials. ^cIL-10 is usually anti-inflammatory, but upon priming of monocytes with IFN α it induces proinflammatory responses.

Besides a soluble form of IL-6R α , a soluble form of gp130 (sgp130) has been detected in healthy human sera with antagonistic properties. Of interest, the antagonistic activity of sgp130 is markedly enhanced in the presence of sIL-6R α [17]. Cell responses to IL-6 are therefore finely tuned by the ratios between-cell bound gp130 and IL-6R α on the one side, and on the other by available IL-6, sIL-6R α and sgp130.

Balance generated by soluble osteoprotegerin

Another cytokine whose biological activities are modulated by soluble receptors or natural antagonists is osteoprotegerin, which is a secreted member of the TNF receptor family that binds OPGL and blocks its activity. Genetic (including gene-targeting) studies and functional studies *in vitro* and *in vivo* indicate that osteoprotegerin is a pure, soluble decoy receptor [18]. Osteoprotegerin also binds and neutralizes TNF- α -related apoptosis-inducing ligand [19].

Additional cytokines whose biological activities are regulated by the balance of agonist and soluble nonsignaling receptors include IL-18/IL-18 binding protein, IL-22/IL-22 binding protein, and IL-13/IL-13 receptor alpha. These will not be discussed in the present review, however, owing to the shortage of space.

Balance in chemokine responses

A balance in chemokine responses is generated via several distinct, but not mutually exclusive, operational mechanisms.

As previously shown for other cytokines, distinct chemokines may fulfill opposing functions for a given task. A classical example is the propensity of CXC chemokines sharing the ELR motif (CXCL1, CXCL3, CXCL5, CXCL6, and CXCL8) to exert angiogenic properties, while CXC chemokines lacking the ELR motif (CXCL9, CXCL10, CXCL11) are more angiostatic [20]. Similarly, chemokines may play opposing roles in proliferation and apoptosis susceptibility. In addition, a peculiarity of some chemokine receptors is that they bind chemokines but fail to signal [21]. Chemokines signal through seven-transmembrane domain, G-protein-coupled receptors, of which 19 have been molecularly defined. These receptor families reflect the two major (CC and CXC) chemokine families and two minor (C and CX₃C) chemokine families [22]. In addition, chemokine receptors whose structural features are inconsistent with signaling functions have been described. By binding to chemokines, non-signaling receptors act as a decoy, scavenge receptors, and regulate inflammatory and immune responses. The family of silent chemokine receptors comprises Duffy antigen receptor for chemokines (DARC), D6 (also known as CC chemokine binding protein 2), and CCX-CKR (also known as CCRL1). It is noteworthy that the silent chemokine receptors, which lack the key residues needed for coupling with G-proteins, have unusual expression patterns and a wide range of chemokine-binding properties.

DARC is expressed on erythrocytes and endothelial cells of postcapillary veins in many organs – including, amongst others, high endothelial venules in lymphoid organs [23]. DARC binds 11 proinflammatory (both CC and CXC) but not homeostatic chemokines, and preferentially angiogenic but not angiostatic chemokines [24]. Chemokines injected in DARC^{-/-} mice rapidly disappear from circulation, indicating a role of erythrocyte DARC as a sink or reservoir. Endothelial DARC, however, appears to have a downregulating effect on inflammation. Overexpression of endothelial DARC in animal models is therefore associated with both decreased angiogenesis and tumor growth, while a lack in DARC is associated with increased tumor growth, metastasis formation and increased concentrations of CXCL1 and CXCL3 [25,26].

D6 binds most inflammatory CC chemokines, but not CXC and homeostatic CC chemokines. D6 is expressed at high concentrations on lymphatic and venular endothelium, particularly in the skin, gut, lung, and placenta [27]. D6 mediates chemokine degradation, being constitutively internalized through clathrin-coated pits. D6^{-/-} mice are prone to exaggerated inflammatory responses induced by phorbol ester myristate acetate application to the skin or subcutaneous injections of complete Freund's adjuvant [28,29]. Lack of D6 expression in syncytiotrophoblast increases the susceptibility to inflammation-induced fetal loss [30]. In contrast, transgenic expression of D6 in keratinocytes dampens cutaneous inflammation and reduces tumor growth [31].

CCX-CKR appears to have a more limited chemokine-binding repertoire that includes CCL19, CCL21, CCL25, and CXCL13, and it is expressed exclusively by stromal cells in the thymus and lymph nodes, by lymph vessels in the intestine and by the epidermis [32]. In CCX-CKR^{-/-} mice, trafficking of dendritic cells to lymph nodes under steady-state conditions appears to be decreased, as well as the recruitment of hematopoietic precursors to the thymus.

Pathogen-encoded decoys also affect chemokine activities. Indeed, molecular mimicry of chemokines and their receptor is an important immune-evasion strategy used by pathogens, of which numerous examples are known. Viral chemokine binding protein and *Schistosoma mansoni* chemokine binding protein have been described.

The receptor functions of some chemokines appear to vary according to the context in which they operate. For instance, IL-10 uncouples CCR2 binding from signaling, and therefore CCR2 functionally becomes a decoy receptor [33]. An additional example is the high level of CCR5 expressed in response to lipoxin A4 on apoptotic neutrophils and T cells. Lipoxin A4 is produced late during the inflammatory response when significant tissue damage has already occurred. By increasing the expression of CCR5 on dying cells, lipoxin A4 contributes to scavenging CCR5 ligands, which therefore are no longer available for recruiting new cells, which in turn reduces inflammation.

An additional mechanism regulating chemokine activities is related to modifications of their primary structure. For instance, the N-terminal natural deletion variant of monocytes chemotactic protein-1/CCL2 (called 7ND) inhibits chemotaxis mediated by monocytes chemotactic protein-1, and the extension of RANTES/CCL5 by a single methionine (met-RANTES) creates a potent and selective RANTES antagonist.

The particular example of chemerin

Chemerin is a plasma protein known for its proinflammatory properties exerted upon binding to the G-protein coupled receptor ChemR23/CMKLR1 – expressed on macrophages and plasmacytoid dendritic cells – where it induces cell migration. Chemerin is secreted as an inactive precursor and is processed by proteases before becoming an active mediator. As for conventional chemokines, the biologically active chemerin binds to ChemR23 with its COOH-terminal portion.

Of interest, different proteases generate different chemerin peptides, which possess opposite functions. Serine proteases mainly produced by activated neutrophils – early mediators in inflammation – therefore generate chemerin 9 (9 AA peptide), which is an agonist in the nanomolar range. Cysteine proteases – mainly produced by macrophages – which arrive later at the inflammatory site, however, generate chemerin 15 (15 AA peptide). This peptide in the picomolar

range acts as an antagonist, expressing potent anti-inflammatory activities and contributing to reduce inflammation [34].

A further layer of complexity has been added recently with the description of an additional chemerin receptor named CCRL2, selectively expressed on mouse mast cells. Upon binding to this receptor, chemerin induces neither cell migration nor calcium flux. CCRL2 is therefore supposed to scavenge chemerin. The experimental test of this hypothesis led to the opposite result, however, indicating enhanced inflammation in a rodent model of IgE-mediated passive cutaneous anaphylaxis. A possible explanation could be that mast cells bind the N-terminal portion of chemerin with CCRL2 and present the COOH-terminal portion to cells expressing ChemR23, which are thus potently activated [35].

The Th1/Th2 balance

In the late 1980s Mosmann and colleagues described the Th1/Th2 balance when studying a large series of mouse CD4⁺ T-cell clones [36]. They observed that some clones would produce IFN γ but not IL-4, while others would do the opposite. Therefore, based on the dichotomic production of two key cytokines, it was possible to classify T-cell clones into two groups, which were named Th1 and Th2. The same concepts were verified by studying human T-cell clones [37]. Naïve T cells could be induced to become Th1 or Th2 simply by modifying the cytokine present in the milieu during priming, although the dose of antigen, the amount of co-stimulation, and the age of antigen-presenting cells could also affect polarization.

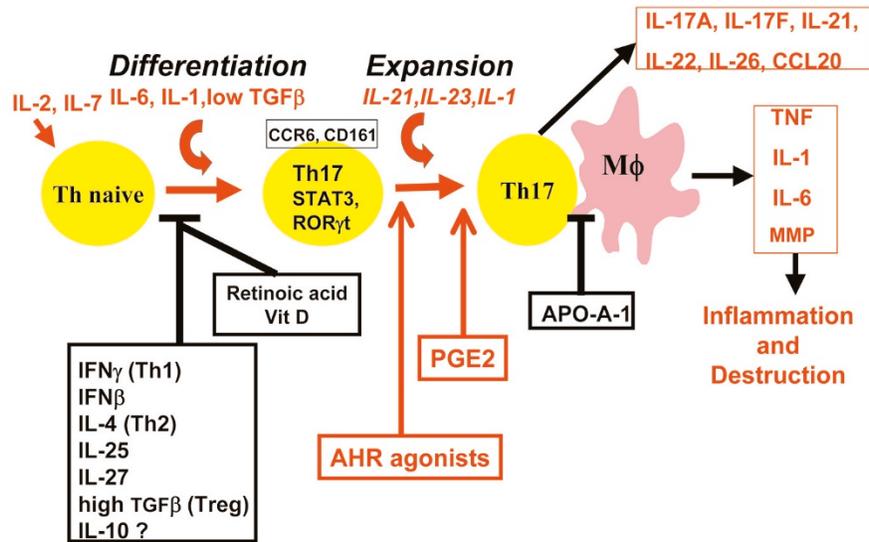
Of major importance, Th1 cytokines were shown to inhibit Th2 cytokine production and function, and *vice versa*. This observation included cytokines important for priming: IL-12 and IFN γ for Th1 cells, and IL-4 for Th2 cells. Starting investigations with mouse models of human diseases, it was found that models of multiple sclerosis – such as the antigen-induced experimental acute encephalomyelitis (EAE) – or of RA – such as type II collagen arthritis – were associated with the overexpression of IFN γ but not of IL-4. In sharp contrast, models of allergic diseases such as asthma were associated with IL-4 without IFN γ expression. In these models, forced expression of counteracting T-helper cytokines could in many instances abrogate disease expression [38,39].

Addition of the Th17 pattern

In 2005 the above classification was amended when it was shown in the mouse that IL-17 was produced by a particular T-helper cell, named Th17 [40,41] (Figure 3). As early as 1999, however, it was shown that some T-cell clones obtained from the synovium of RA patients were producing IL-17 and differed from the classical Th1/Th2 clones [42]. Indeed, they did not produce IL-4 and produced little, if any, IFN γ .

The Th1/Th2 paradigm was then revisited; key observations were made based on the murine EAE model [43]. This model

Figure 3



Cytokines, hormones, and other soluble mediators controlling biology of Th17 cells leading to tissue destruction. Summary of some of the many mediators involved in Th17 differentiation, expansion, acquisition of effector function and their relationship with macrophages, which may then mediate tissue destruction. Orange arrows, enhancement; blunted black heads, inhibition; black arrows, production. AHR, aryl-hydrocarbon receptor; APO-A-1, apolipoprotein A1; MMP, matrix metalloproteinase; MΦ, macrophage; PGE2, prostaglandin E₂; RORγt, retinoic acid-related orphan receptor γt; STAT, signal transducer and activator of transcription; TGFβ, T-cell growth factor beta; Treg = T cell with regulatory function.

was previously associated with Th1 responses. Th1 cells are induced by IL-12 produced by monocytes and dendritic cells. IL-12 is a heterodimer composed of p35 and p40 subunits. Protection from EAE was afforded when IL-12 was blocked with anti-IL-12p40. IL-23 is also a heterodimer, however, composed of the IL-12/IL-23 common p40 subunit and the specific p19 subunit. When inhibitors specific to IL-23 or p19-deficient mice were used, it was recognized that IL-23 and not IL-12 was responsible for EAE induction by assisting the expansion of Th17 cells. Many chronic inflammatory diseases previously thought to be associated with Th1 have therefore been reclassified as Th17 diseases [44]. The opposing roles of Th2 and Th17 responses are now clear, since IL-4 strongly inhibits IL-17 differentiation. For Th1 and Th17 cells, a more balanced view is now accepted [45]. In both human and murine conditions, a large proportion of T cells can express simultaneously IFNγ and IL-17. This is clearly seen with T-cell clones from peripheral blood. The simultaneous production of the two cytokines appears uncommon, however, in inflammatory tissues where T cells producing cytokines take on a plasma cell-like appearance, possibly indicating full differentiation with a fixed phenotype [46].

In addition to the production of IL-17 (now referred to as IL-17A), Th17 cells can produce other cytokines – including IL-17F (a close member of the IL-17 family), IL-21, and IL-22. IL-21 acts as an endogenous amplifier of the Th17 lineage [41]. IL-22 appears more specifically associated with skin defense [47]. IL-17A and IL-17F share a large number of

functions, with a strong correlation between the genes induced in RA synoviocytes by the two cytokines, IL-17F being less potent [48]. In addition, synergistic activities are seen when combining TNF with IL-17A or IL-17F. IL-17A and IL-17F may, however, have different roles in mouse models of inflammation and host defense [49].

IL-17E (also termed IL-25) is a very different member of the IL-17 family. IL-17E is more a Th2 cytokine, involved in allergic reactions and inhibiting the Th17 pathway [50]. Consequently, there is another balance between the effects of IL-17A and IL-17F and those of IL-17E/IL-25.

Balance between Th17 and T cells with regulatory function

Th1, Th2, and Th17 cells are effector cells contributing to key functions of the immune response. An additional heterogeneous subset of T cells with regulatory function (Tregs) has recently been identified. Some Tregs occur naturally, whereas others are induced in response to antigens. Characteristically, Tregs express the transcription factor Foxp3, as well as CD4 and CD25. The immunomodulating effects of Tregs are mediated by membrane molecules (for example, cytotoxic T-lymphocyte-associated protein 4, glucocorticoid-induced TNF receptor, and OX40) and by cytokines including IL-10 and TGFβ.

TGFβ is key to the induction of Foxp3-positive regulatory T cells. Indeed, mice defective in TGFβ die quickly from a

massive uncontrolled inflammatory disease [51]. Contrasting with the effect of TGF β alone, the simultaneous presence of TGF β and IL-6 favors the emergence of Th17 cells alongside the inhibition of the Tregs [52]. IL-6 – a cytokine with pleiotropic inflammatory effects – therefore plays a pivotal part, at least in the mouse, in directing the differentiation of T cells toward the Th17 or Treg pathways. TNF, IL-1, and IL-17 interact together to induce massive amounts of IL-6. Increased inflammation therefore has a positive effect on the Th17 pathway and a negative effect on its regulation.

The inhibitory functions of IL-27 and IL-35

Some recently identified cytokines such as IL-27 and IL-35 appear to be more involved in dampening the immune response. IL-27 belongs to the IL-12 cytokine family that also comprises IL-23 and IL-35, all involved in the regulation of T-helper cell differentiation. IL-27 is unique in that it induces Th1 differentiation while simultaneously suppressing immune responses. The immunosuppressive effects of IL-27 depend on inhibition of the development of Th17 cells and induction of IL-10 production [53]. IL-27 exerts potent anti-inflammatory effects in several infectious and experimental autoimmune models. In particular, suppressive effects on helper T cells – which are implicated in the pathogenesis of multiple sclerosis – suggest that IL-27 may be therapeutically relevant in multiple sclerosis. While exciting discoveries have been made, however, these are still at an early stage and further studies are required to understand the pathophysiological roles of IL-27 and its therapeutic potential in humans [54].

The inhibitory cytokine IL-35 contributes to regulatory T-cell function, being specifically produced by Tregs and required for maximal suppressive activity [55]. Ectopic expression of IL-35 confers regulatory activity on naive T cells, whereas recombinant IL-35 suppresses T-cell proliferation. The role of Tregs in RA has been established in both patients and animal models. The Tregs increase in patients who are responding to anti-TNF α therapy. Of the current hypotheses, Treg expansion or transfer may hold promise for the treatment of RA [56].

Cytokines, hormones, vitamins, arachidonic acid metabolites and lipoproteins

A further layer of control at the level of expression of cytokines, cytokine inhibitors and acute-phase proteins is provided by hormones. Estrogens as well as androgens inhibit the production of IL-1 β and TNF α by monocytes–macrophages. Androgens antagonize stimulatory effects of estrogens. Some studies suggest that estradiol is more inhibitory to Th1 cytokines (for example, IFN γ , IL-2) while testosterone is inhibitory to Th2 cytokines (for example, IL-4). On the other hand, cytokines control the hypothalamic–hypophyseal–adrenal gland axis as well as the sex hormones [57]. Vitamins may also affect cytokine production by influencing the polarization of effector CD4⁺ T cells. For instance, retinoic acid enhances Treg expansion while simul-

taneously inhibiting Th17 cells [58]. Conversely, vitamin D favors Th2 polarization and diverts Tregs from their regulatory function [59,60]. Finally, prostaglandin E₂ – a metabolite of arachidonic acid – may also affect cytokine production by favoring the expansion of Th17 cells [61].

Destruction/repair balance

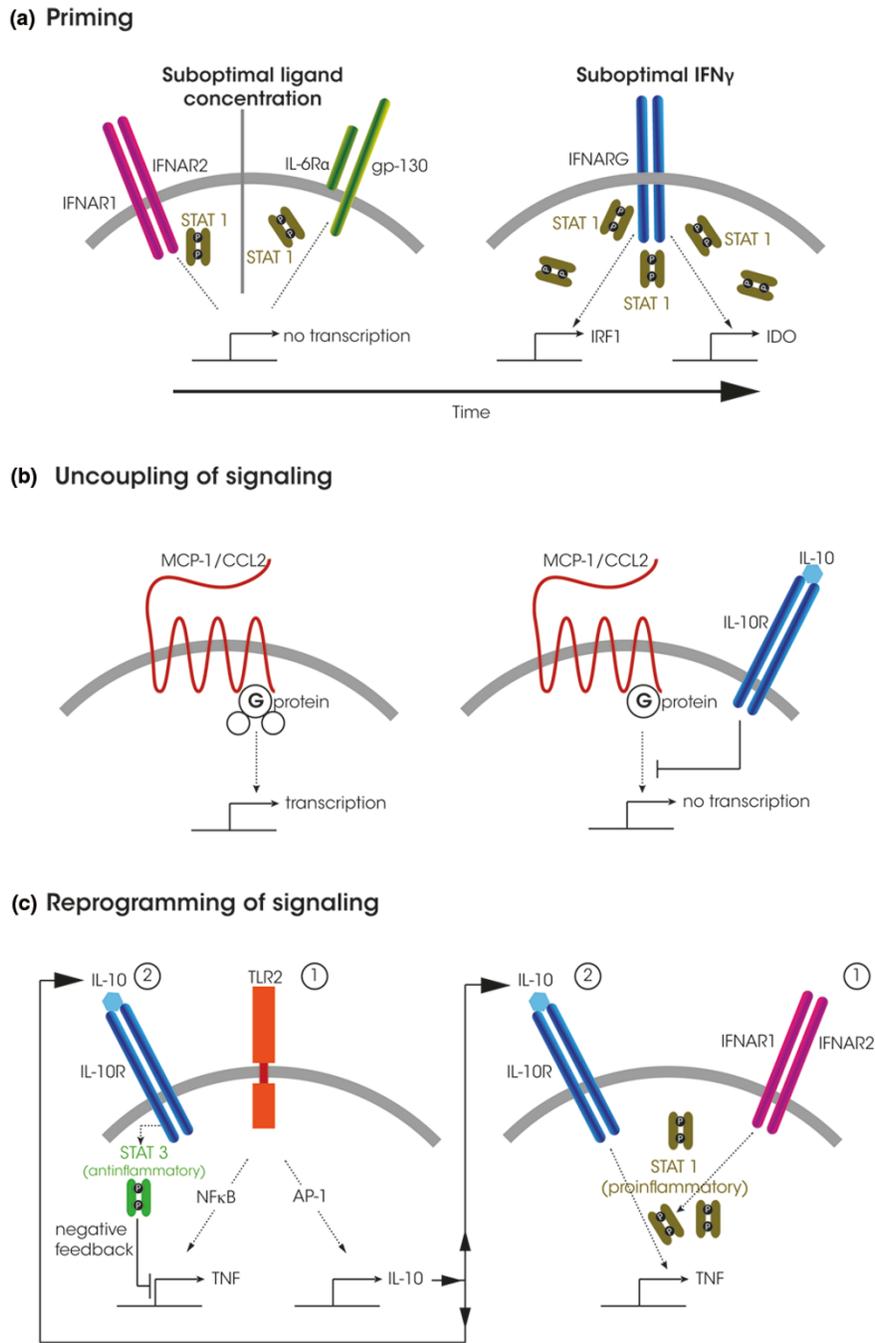
Chronic inflammatory diseases such as RA are so severe because the disease process affects matrix metabolism. Although RA is seen as a destructive disease, it is not well appreciated that the main problem is in fact the inhibition of repair activity. Any type of chronic joint inflammation, whether infectious, inflammatory, or autoimmune, will result in joint destruction within months or, at best, within a few years, but it will take decades to observe some kind of joint repair – even in conditions like osteoarthritis where repair activity is maintained. In a model of cell interaction between synovocytes and T-cell clones, it was found that Th1 and Th17 clones induced defects in collagen synthesis *in vitro*, indicating an inhibition of their repair activity (Figure 1). In sharp contrast, Th2 cells induce collagen synthesis, indicating their beneficial role in repair activity [62]. Very similar conclusions were obtained when monocytes were incubated with Th1 or Th2 clones. The interaction with a Th1 clone led to the production of IL-1, a key marker of destructive inflammation, whereas the use of a Th2 clone led to production of IL-1Ra along with its anti-inflammatory and anti-destructive properties [63].

Wingless integration site (Wnt) proteins make up a family of secreted growth factors, identified in virtually every organism; they regulate key aspects of cellular functions such as growth, differentiation, and death. Several members of the Wnt pathway play an important part in bone remodeling. Dickkopf-1, a soluble inhibitor of the Wnt pathway, controls bone remodeling. Increased Dickkopf-1 levels are linked to bone resorption, and decreased levels are linked to new bone formation. Low-density lipoprotein receptor-related protein 5, the main receptor that mediates Wnt signaling, plays a critical role in bone mass regulation. Gain-of-function mutations of lipoprotein receptor-related protein 5 cause high bone mass phenotypes, whereas loss-of-function mutations are linked to severe osteoporosis [64].

Adipose tissue in inflammation: a protective role via IL-1 receptor antagonist?

Adipokines are beginning to emerge as mediators of inflammation. Knowledge of their precise activities remains in its infancy, however, and is still controversial [65]. Many of the adipokines appear to have proinflammatory properties. In general, adiponectin is considered anti-inflammatory, and leptin, visfatin and resistin are considered proinflammatory. The formation of adipose tissue could be due to abnormal metabolic processes and, at the local level, due to chronic inflammatory processes such as those occurring in the synovium in RA or osteoarthritis, or in the peritoneal cavity in various inflammatory processes of the digestive system.

Figure 4



Schematic examples of cytokine signal modulation. **(a)** Priming: upon exposure to suboptimal levels of type I interferon or IL-6, no signal is generated; but if later the cell (macrophage) sees suboptimal levels of IFN γ , then gene transcription initiates and a signal is generated [67,68]. IDO, indoleamine-2,3-dioxygenase; IFNAR, interferon alpha receptor IL-6Ra, IL-6 receptor alpha; IRF1, interferon regulatory factor 1; STAT, signal transducer and activator of transcription. **(b)** Uncoupling of signaling: monocytes chemotactic protein-1 (MCP-1)/CCL2 signal upon CCR2 binding. In the presence of IL-10, binding of MCP-1/CCL2 to CCR2 is preserved but signal is abolished [33]. IL-10R, IL-10 receptor. **(c)** Reprogramming of signaling: in macrophages, Toll-like receptor (TLR) 2 activation induces TNF, production of which is reduced by simultaneously induced homeostatic IL-10 (negative feedback). If the cell has been primed with type I interferon, however, then IL-10 fails to negatively regulate TLR signaling. In turn, IL-10 becomes a proinflammatory cytokine favoring the production of TNF and other cytokines. The signaling cascade induced by IL-10 shifts from anti-inflammatory STAT 3 to proinflammatory STAT 1 [70]. Figures in circles indicate sequences of events. AP-1, activator protein 1.

Adipocytes are said to produce many hormones and pro-inflammatory mediators. White adipose tissue in humans, however, is assumed to be the main source of IL-1Ra, and also contains IL-10. Furthermore, IFN β was found to be the principal cytokine inducing IL-1Ra in various white adipose tissues, such as that present in the synovium. It is possible that, in addition to other functions, adipose tissue may be part of a mechanism limiting local inflammation and that fibroblasts in the vicinity may further induce IL-1Ra in adipocytes via the production of IFN β [66].

Influence of signal transduction in cytokine balance

Cytokines may have opposing effects on the same cell depending on the circumstances in which they hit their target. The timing and the previous activation status are major determinants of responses that cytokines elicit (Figure 4). Differential outcomes could be sensitization or amplification of proinflammatory signals (that is, priming), reprogramming of signaling resulting in proinflammatory activity of pleiotropic or anti-inflammatory cytokines, and attenuation of anti-inflammatory signals and homeostatic mechanisms. Signal transducer and activator of transcription (STAT) 1 has been shown *in vitro* and *in vivo* to be involved in some of these effects. For instance, transient exposure to subactivating concentrations of IFN α or IL-6 primes primary human monocytes for subsequent exposure to IFN γ , resulting in enhanced interferon regulatory factor 1 and indoleamine-2,3-dioxygenase gene expression in a STAT-1-dependent manner [67,68]. This may explain robust IFN signatures in RA synovium, notwithstanding very low amounts of IFN γ . Enhanced expression of STAT-1-dependent genes upon IFN γ priming of monocytes is a finely tuned process involving Fc γ receptor/DNAX activation protein 12, as demonstrated in Fc γ receptor/DNAX activation protein 12^{-/-} mice in which the priming effect is lost.

IL-10 contributes to homeostatic responses in proinflammatory conditions. For instance, in human monocytes, Toll-like receptor 2 ligation results in NF κ B-dependent TNF production and simultaneously in activator protein-1-dependent IL-10 production [69]. Upon binding to its receptor, IL-10 decreases TNF production in a STAT-3-dependent manner, thus exerting a negative feedback. Pre-exposure of monocytes to IFN α , however, results in IL-10 gaining pro-inflammatory functions. Of interest, this process is STAT 1 dependent. It has therefore been shown in human monocytes primed with IFN α that IL-10 not only fails to reduce the subsequent production of TNF in response to lipopolysaccharide, which may simply indicate a loss of function of the anti-inflammatory activity of IL-10, but in addition primes monocytes to transcribe genes in response to IL-10 usually induced by IFN. It appears that, due to the effect of type I interferons, the balance of IL-10 signaling shifts from STAT 3 (anti-inflammatory) to STAT 1 (proinflammatory) signals. Furthermore, IL-10 induces chemokine production in IFN α -

primed macrophages, resulting in recruitment of activated T cells; aberrant IL-10 signaling may therefore contribute to inflammation in conditions with high interferon levels (systemic lupus erythematosus) [70].

The suppressors of cytokine signaling (SOCS) family of intracellular proteins – which encompasses eight members, sharing a central Src homology domain 2 and a C-terminus SOCS box – act as negative regulators of intracellular signaling of the Jak–STAT pathway used by several cytokines. They act by inhibiting the kinase activity, by competing with substrates needed for signal transduction, and by targeting associated proteins to proteasome degradation. Beside negative regulation, SOCS proteins can also affect the quality of signaling. For instance, in the absence of SOCS 3, IL-6 induces a wider transcriptional response, which includes interferon-like gene expression owing to increased STAT 1 phosphorylation. SOCS proteins therefore impact on a number of important mechanisms regulating inflammation and the immune response [71].

Conclusions

Cytokine activities affect most, if not all, biological processes involved in homeostasis as well as in host defense and auto-aggression. A continuous, finely tuned, crosstalk between cytokines, receptors, agonist and antagonist ligands, as well as with mediators belonging to other families of molecules, regulates cytokine biological activities. Furthermore, the context in which cytokines are available, including the temporal sequence of events preceding the availability of a given cytokine, very much impact on their capacity to favor or inhibit inflammation and other biological processes. During the past three decades we have learned that an imbalance in cytokine activities is associated with autoimmune and autoinflammatory disorders. More important, our knowledge of the many levels of cytokine balance has led to the generation of important tools to control inflammatory and destructive diseases. The future will no doubt witness additional major achievements in this area of medicine.



The Scientific Basis of Rheumatology: A Decade of Progress

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Competing interests

The authors declare that they have no competing interests.

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