Abstract
The multitude and abundance of macrophage-derived mediators in rheumatoid arthritis and their paracrine/autocrine effects identify macrophages as local and systemic amplifiers of disease. Although uncovering the etiology of rheumatoid arthritis remains the ultimate means to silence the pathogenetic process, efforts in understanding how activated macrophages influence disease have led to optimization strategies to selectively target macrophages by agents tailored to specific features of macrophage activation. This approach has two advantages: (a) striking the cell population that mediates/amplifies most of the irreversible tissue destruction and (b) sparing other cells that have no (or only marginal) effects on joint damage.

Introduction
Macrophages (Mφ) are of central importance in rheumatoid arthritis (RA) due to their prominent numbers in the inflamed synovial membrane and at the cartilage-pannus junction, their clear activation status [1,2] (see Table 1 for overview), and their response to successful anti-rheumatic treatment [3]. Although Mφ probably do not occupy a causal pathogenetic position in RA (except for their potential antigen-presenting capacity), they possess broad pro-inflammatory, destructive, and remodelling potential and contribute considerably to inflammation and joint destruction in acute and chronic RA. Also, activation of this lineage extends to circulating monocytes and other cells of the mononuclear phagocyte system (MPS), including bone marrow precursors of the myelomonocytic lineage and osteoclasts [2,4,5].

Thus, before a causal factor for RA is known, monocytes/Mφ remain an attractive research focus for the following reasons:

(a) the radiological progression of joint destruction correlates with the degree of synovial Mφ infiltration [1], (b) the therapeutic efficacy of conventional anti-rheumatic therapy coincides with downregulation of MPS functions [6], (c) therapies directed at cytokines made predominantly by Mφ are effective in RA [7], (d) conventional or experimental drugs can be selectively targeted to Mφ or their different subcellular compartments (for example, [2,8]), (e) differential activation of intracellular signal transduction pathways underlies different Mφ effector functions [9], and (f) more specific inhibitors of key metabolic enzymes or particular signal transduction pathways may become available as selective targets of anti-rheumatic therapy [9,10]. In addition, the amplifying role of Mφ in RA has emerged so clearly that the effects of anti-rheumatic therapy (whether specific or conventional) on monocytes/Mφ may become an objective readout of the effectiveness of treatment [11-13] (Stuhlmüller B, Hernandez MM, Haeupl T, Kuban RJ, Gruetzkau A, Voss JW, Salfeld J, Kinne RW, Burmester GR, unpublished data).

Differentiation and activation of the mononuclear phagocyte system in rheumatoid arthritis
Cells of the myelomonocytic lineage differentiate into several cell types critically involved in disease (that is, monocytes/Mφ, osteoclasts, and dendritic cells) (Figure 1a). Due to their marked plasticity, these pathways can be influenced by an excess/imbalance of cytokines or growth factors, resulting in altered differentiation/maturation (Figure 1b). In RA, such imbalances clearly occur in inflamed joints, peripheral blood, and bone marrow (Table 2 and Figure 1b).
Cells of the MPS show clear signs of activation, not only in synovial and juxta-articular compartments such as the synovial membrane or the cartilage-pannus and bone-pannus junctions (including the subchondral bone), but also in extra-articular compartments (for example, peripheral blood and subendothelial space, the latter of which is the site of foam cell formation and development of atherosclerotic plaques in RA) (Table 2). This activation underlines the systemic inflammatory character of RA and may contribute to the occurrence of cardiovascular events and its increased mortality (reviewed in [2,14,15]).

**Table 1**

| Class of overexpressed molecules                                      | Molecules                                                                 | Known or potential function                                                                                                                                 |
|-----------------------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Class II major histocompatibility complex (overexpressed on Mφ)      | HLA-DR                                                                    | Presentation of antigens relevant to disease initiation or severity [93] (Stuhlmüller B, et al., unpublished data) (reviewed in [2])                |
| Cytokines and growth factors                                          | For example, TNF-α, IL-1, IL-6, IL-10, IL-13, IL-15, IL-18, migration inhibitory factor, granulocyte macrophage colony-stimulating factor, and thrombospondin-1 | Mediation and regulation of local and systemic inflammation and tissue remodelling (reviewed in [2,24,39,82])                                           |
| Chemokines and chemoattractants                                      | For example, IL-8, macrophage inflammatory protein-1, monocyte chemoattractant protein-1, and CXCL13 | Mediation and regulation of monocyte migration                                                                                                                                                                        |
| Metalloproteases (MMPα)                                              | MMP-9 and MMP-12                                                          | Tissue degradation and post-injury tissue remodelling [94,95]                                                                                                                                                    |
| Tissue inhibitors of MMP (TIMPα)                                      | TIMP-1                                                                    | Attempt to control excessive tissue destruction [96]                                                                                                                                                              |
| Acute-phase reactants                                                | For example, C-reactive protein and A-SAA (serum amyloid A)              | Integrated hormone-like activation of hepatocytes by synovial Mφ and fibroblasts (mostly via IL-6) [97] (reviewed in [2])                                |
| Other molecules                                                      | Neopterin                                                                 | Produced by interferon-gamma-stimulated monocytes/Mφ                                                                                                                                                             |
|                                                                       |                                                                          | Induces/enhances cytotoxicity and apoptosis                                                                                                                                                                       |
|                                                                       |                                                                          | Acts as antioxidant [98,99]                                                                                                                                                                                        |
|                                                                       | Cryopyrin                                                                 | Produced by TNF-α-stimulated Mφ                                                                                                                                                                                     |
|                                                                       |                                                                          | Regulates nuclear factor-kappa-B and caspase-1 activation [100]                                                                                                                                                  |

IL, interleukin; Mφ, macrophages; TNF-α, tumor necrosis factor-alpha. Reproduced with permission from Kinne RW, Stuhlmüller B, Palombo-Kinne E, Burmester GR: The role of macrophages in rheumatoid arthritis. In *Rheumatoid Arthritis*. Edited by Firestein GS, Panayi GS, Wollheim FA. New York: Oxford University Press; 2006:55-75 [2].

**Stimulation/regulation of monocyte/macrophage activation in rheumatoid arthritis**

The role of monocytes/Mφ in RA is conceivably the integrated result of stimulatory, effector, dually active, and autoregulatory mediators/mechanisms. At the tissue level, the scenario is characterized by the influx of pre-activated monocytes, their maturation into resident Mφ, their full activation, and their interaction with other synovial cells. The complexity of the interaction is the result of paracrine activation mechanisms generated via sheer cell-cell contact as well as of numerous autocrine mechanisms - nearly any soluble mediator shows abnormalities. A simplified scheme of this integrated system and the currently known mediators is provided in Figure 2. For ease of presentation, the parts are organized as incoming stimuli (both paracrine and soluble) (column a) and effector molecules (column b), although autocrine loops are also relevant (as discussed below).

**Cell-cell interaction**

A significant part of Mφ effector responses is mediated by cell contact-dependent signalling with different inflammatory or mesenchymal cells (as exemplified in the lower left quadrant of Figure 2).
Fibroblast-macrophage interaction
Because of the prominent numbers of Mφ and fibroblasts and their activated status in RA synovial tissue, the interaction of these cells is critical for the resulting inflammation and tissue damage. Indeed, the mere contact of these cells elicits the production of interleukin (IL)-6, granulocyte macrophage colony-stimulating factor (GM-CSF), and IL-8. The cytokine output can be enhanced or down-modulated not only by addition of pro-inflammatory or regulatory cytokines (for example, IL-4, IL-10, IL-13, or IL-1 receptor antagonist [IL-1RA]),
but also by neutralization of the CD14 molecule [17]. Also, in vitro, significant cartilage degradation occurs in co-cultures of mouse fibroblasts and Mφ, a response markedly exceeding that observed with each culture alone (reviewed in [2]). Furthermore, purified human synovial fibroblasts co-cultured with myelomonocytic cells induce cartilage degradation in vitro, but with a strong contribution of soluble IL-1 and tumor necrosis factor (TNF)-α [18].

**T cell-macrophage interaction**

Accessory, inflammatory, effector, and inhibitory Mφ functions can be stimulated by fixed T cells or their plasma membranes if T cells are pre-activated and express activation surface molecules. In response to such interaction, monocytes produce metalloprotease (MMP), IL-1α, and IL-1β [19,20]. Also, T cells pre-stimulated in an antigen-mimicking fashion stimulate TNF-α and IL-10 production once in contact with monocytes [20]. Conversely, fixed T cells stimulated in an antigen-independent manner (that is, with IL-15, IL-2, or a combination of IL-6 and TNF-α, the so-called Tck cells) induce monocyte production of TNF-α but not the anti-inflammatory IL-10 [20,21]. These findings suggest that early RA may reflect antigen-specific T cell-Mφ interactions [22]. Conversely, chronic RA may be associated with antigen-independent interactions dominated by an exuberant cytokine milieu and Tck cells. This may also explain the relative paucity of IL-10 in the synovial membrane in chronic RA, as discussed below.

Several ligand pairs on T cells and monocytes/Mφ have been implicated in this interaction [20], although the importance of individual ligand pairs, as well as the influence of soluble mediators, remains unclear. Interestingly, T cells isolated from RA synovial tissue show phenotypical and functional features similar to Tck cells and the above-mentioned signal transduction pathways differentially contribute to the induction of TNF-α and IL-10 production in monocytes/Mφ by co-culture with Tck cells. If applicable in vivo in RA, this would allow selective therapeutic targeting of pro-inflammatory TNF-α and sparing of anti-inflammatory IL-10.

**Interaction of macrophages with endothelial cells and natural killer cells**

The interaction between monocytes and endothelial cells in RA (Figure 2), critical for the sustained influx of activated monocytes in the synovial membrane, relies on the altered expression of integrin/selectin pairs on the surface of the two cell types (reviewed in [2]). Because the synovial cytokine milieu (including the Mφ-derived TNF-α) upregulates the expression of these ligand pairs, a self-perpetuating cycle ensues by which sustained Mφ-derived mechanisms lead to further influx and activation of circulating monocytes. Upon cell contact, monokine-activated CD56bright natural killer cells induce monocytes to the production of TNF-α, thus representing another possible reciprocal loop of activation in RA [23].

**Soluble stimuli**

Cytokine stimuli with pro-inflammatory effects on macrophages Numerous cytokines with known or potential stimulatory activity on monocytes/Mφ have been identified, as schematically shown in the upper left quadrant of Figure 2. A systematic list of these stimuli and their known or potential functions is provided in Table 4. Some of these mediators are produced by monocytes/Mφ themselves and therefore activate Mφ in an autocrine fashion, as also exemplified in

### Table 2

| Compartment                | Location                          | Differentiation step                                                                |
|----------------------------|-----------------------------------|--------------------------------------------------------------------------------------|
| Joint or juxta-articular   | Synovial membrane                 | • Recently immigrated monocytes                                                     |
|                            |                                   | • Mφ (M1/M2? [64]; resident/inflammatory? [13])                                     |
|                            |                                   | • Dendritic cells                                                                   |
| Cartilage-pannus junction  |                                   | Mφ                                                                                   |
| Subchondral bone           |                                   | Osteoclasts                                                                         |
| Vascular endothelium       |                                   |                                                                                      |
| Extra-articular            | Peripheral blood                  | Circulating monocytes                                                                |
| Bone marrow                |                                   | • Myelomonocytic precursors                                                         |
|                            |                                   | • Endothelial cells                                                                 |
| Subendothelial space       |                                   | Mφ / foam cells / pericytes                                                         |
| Rheumatoid nodules         |                                   | Epitheloid cells and multinucleated giant cells                                      |
| Lung interstitial space    |                                   | Alveolar Mφ                                                                         |

Mφ, macrophages. Reproduced with permission from Kinne RW, Stuhlmuller B, Palombo-Kinne E, Burmester GR: The role of macrophages in rheumatoid arthritis. In *Rheumatoid Arthritis*. Edited by Firestein GS, Panayi GS, Wollheim FA. New York: Oxford University Press; 2006:55-75 [2].
Table 3

Monocyte/macrophage functions and their (potential) role in rheumatoid arthritis

| Function                                      | Mechanisms                                                                 | (Potential) role in rheumatoid arthritis                                                                 |
|-----------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Clearance of immune complexes                 | Binding of immunoglobulins to Fc receptors (Fc-γ-R I, IIA, IIb, and IIIa)  | Potential clearance of rheumatoid factor but further activation of monocytes/Mφ                                                                           |
|                                               |                                                                           | Opsonization of complexes by complement, leading to binding to Mφ complement receptors and further cell activation [101,102] (reviewed in [2,103]) |
|                                               |                                                                           | Notably, inhibition of monocyte activation by Fc-γ-R IIb [102]                                                                                             |
| Complement activation                          | Binding of complement factors to complement receptors 1 (CD35), 3 (CD11b), and 5a (CD88) | Recognition of activated complement (soluble phase or on immunoglobulin G-immune complexes)           |
| Phagocytosis of particulate antigens          | Conventional (Fc-mediated) → lysosomal degradation and MHC-II antigen processing | Scavenging of debris but potential import of arthritogenic molecules [103]                              |
|                                               |                                                                           | Antigen presentation and activation of CD4+ and CD8+ T cells, possibly relevant to disease initiation or perpetuation (spreading of autoimmunity) (reviewed in [2]) |
|                                               | Coiling phagocytosis → lysosomal degradation and MHC-I antigen processing  | Involved in phagocytosis of Borrelia burgdorferi, active agent of Lyme arthritis (reviewed in [2])     |
| Clearance of intracellular pathogens and apoptotic cells | Removal of pathogens and recognition of apoptotic cells via exposed intracellular membrane components | Induction of Mφ-derived cytokines by bacterial toxins or superantigens [26,28,103]                      |
|                                               |                                                                           | Modulation of Mφ responses by mycobacterial lipoarabinomannan [104,105] or Toll-like receptors [29,106] |
|                                               |                                                                           | Persistence of obligate/facultative intracellular pathogens with arthritogenic potential [107,108]     |
| Antigen processing and presentation           | Enzymatic degradation of antigens and binding of antigenic peptides to MHC molecules and transport to the cell surface | Important cognate functions upon antigen recognition via presentation of antigen on MHC-II molecules [109] and expression of membrane second signal molecules adjacent to T cells (reviewed in [2]) |
| Chemotaxis and angiogenesis                   | Attraction of other inflammatory cells and induction of neo-vascularization | Positive feedback between Mφ-derived cytokines and chemotactic factors (for example, IL-6 and monocyte chemoattractant protein-1) |
|                                               |                                                                           | Promotion of angiogenesis by IL-8 and soluble forms of adhesion molecules (for example, vascular cell adhesion molecule-1 and endothelial-leukocyte adhesion molecule-1) [69] |
| Wound healing                                 | Remodelling of tissue via interaction with fibroblasts                    | Sustained monocyte recruitment at wound injury sites via monocyte chemoattractant macrophage inflammatory protein-1α |
|                                               |                                                                           | Phagocytosis of matrix debris and endogenous production of IL-1, TNF-α, and so on as well as post-injury tissue remodelling (reviewed in [2]) |
| Lipid metabolism                              | Mφ synthesis of prostaglandins (PGs) E2 and I2 Expression of scavenger receptor A (uptake of oxidized low-density lipoprotein) | Pro-inflammatory activity of PGE2 and PGL2 and leukotrienes in rheumatoid arthritis, but also autocrine negative feedback through peroxisome proliferator-activated receptors α and γ (reviewed in [2]) |

IL, interleukin; Mφ, macrophage(s); MHC, major histocompatibility complex; TNF-α, tumor necrosis factor-alpha. Reproduced with permission from Kinne RW, Stuhlmueller B, Palombo-Kinne E, Burmester GR: The role of macrophages in rheumatoid arthritis. In Rheumatoid Arthritis. Edited by Firestein GS, Panayi GS, Wollheim FA. New York: Oxford University Press; 2006:55-75 [2].

Table 4. T-cell cytokines acting on Mφ (for example, IL-17) have been comprehensively reviewed elsewhere [24,25].

Bacterial/viral components and Toll-like receptors

The ability of bacterial toxins or superantigens to initiate the secretion of Mφ-derived cytokines is relevant in view of a possible microorganism etiology of RA and in view of side effects of anti-TNF-α therapy, particularly mycobacterial infections [26,27]. Lipopolysaccharide (LPS), for example, binds to Mφ through the CD14/LPS-binding protein receptor complex and, in vitro, stimulates the production of IL-1β, TNF-α, and macrophage inflammatory protein-1α. Staphylococcal enterotoxin B (SEB), a potent Mφ activator, enhances arthritis in MRL-lpr/lpr mice. Anti-TNF-α therapy, in this case, reverses both the severe wasting effects of SEB and the incidence of arthritis, indicating that TNF-α is central in this system. Finally, the staphylococcal enterotoxin A increases the expression of the Toll-like receptor (TLR)-4 in human
monocytes by ligation of major histocompatibility complex-II, with subsequent enhancement of pro-inflammatory cytokines by known TLR-4 ligands (for example, LPS [28]).

TLRs are part of the recently discovered cellular pattern-recognition receptors (PPRs) involved in first-line defense of the innate immune system against microbial infections. In addition to bacterial or viral components, some PPRs recognize host-derived molecules, such as the glycoprotein gp96, nucleic acids, hyaluronic acid oligosaccharides, heparan sulfate, fibronectin fragments, and surfactant protein A (reviewed in [29]). In RA, notably, functional TLR-2 and TLR-4 are expressed on CD16+ synovial Mφ, peripheral blood mononuclear cells, and synovial fibroblasts [30]. Also, their expression can be upregulated by cytokines present in the inflamed RA joint (for example, IL-1β, TNF-α, macrophage colony-stimulating factor, and IL-10); this suggests that activation of synovial cells via TLRs may contribute to disease processes [29], as supported by findings in experimental arthritis [31]. On the other hand, the chronic polyarthritis observed in mice with deletion of the DNase II gene, whose Mφ are incapable of degrading mammalian DNA, appears to occur independently of the nucleic acid-specific TLR-9 [32].
### Table 4

**Overview of pro-inflammatory interleukins relevant to macrophage (dys)function in rheumatoid arthritis**

| Family | Cytokine | Pro-inflammatory | Dual | Autocrine | Main pathogenetic features |
|--------|----------|------------------|------|-----------|-----------------------------|
| IL-1   | IL-1     | X                | -    | X         | Predominantly produced by Mφ  |
|        |          |                  |      |           | Critical mediator of tissue damage |
|        |          |                  |      |           | Possesses autocrine features [43, 51-53] |
| IL-18  | X        | -                | X    |           | Predominantly produced by Mφ  |
|        |          |                  |      |           | Critical pleiotropic mediator of disease |
|        |          |                  |      |           | Possesses autocrine features [59-61] |
| IL-33  | X        | X                | -    |           | Produced by endothelial cells |
|        |          |                  |      |           | Important Th2-inducing component in allergy/autoimmunity |
|        |          |                  |      |           | Signals via IL-1 receptor-related protein (ST2) |
|        |          |                  |      |           | Nuclear factor with transcriptional repressor properties (< nuclear factor from high endothelial venules) [111-113] |
| IL-18 inducible | IL-32 | X          | -    | -         | Pro-inflammatory effects on both myeloid and non-myeloid cells [114, 118] |
| IL-2   | IL-7     | X                | -    | -         | Elevated in RA, although a relative paucity is also possible [116, 117] |
|        |          |                  |      |           | Induces osteoclastic bone loss in mice [118] |
| IL-15  | X        | -                | X    |           | Produced by Mφ  |
|        |          |                  |      |           | Important autocrine mediator of disease processes [21, 56-58] |
| IL-21  | X        | -                | -    |           | Only IL-21R is expressed by synovial Mφ and fibroblasts [119] |
| IL-6   | IL-6     | X                | X    | -         | Predominantly produced by fibroblasts under the influence of Mφ  |
|        |          |                  |      |           | Most strikingly elevated cytokine in acute RA, with phase-dependent differential effects [17, 75, 76] (reviewed in [2, 77]) |
| IL-31  | X        | -                | -    |           | Induces experimental dermatitis [120] |
| LIF    | X        | -                | -    |           | Stimulates proteoglycan resorption in cartilage [121] |
| Oncostatin M | X          | -    | -         |         | Recruits leukocytes to inflammatory sites and stimulates production of metalloprotease (MMP) and tissue inhibitor of MMP [121] |
| IFN type I/IL-10 | IL-19 | X          | -    | X         | Involved in both Th1 and Th2 inflammatory disorders [122, 123] |
|        |          |                  |      |           | Possesses autocrine features [124, 125] |
| IL-20  | X        | -                | X    |           | Overexpressed in psoriasis |
|        |          |                  |      |           | Possesses autocrine features [122] |
| IL-22  | X        | -                | -    |           | Relevant to innate immunity and acute-phase response [126] |
| IL-24  | X        | -                | -    |           | Possible antagonism with regulatory IL-10 [127] |
| IL-26  | X        | -                | -    |           | Polymorphism possibly contributes to RA sex-bias susceptibility [128] |
| IL-28, IL-29 | X          | -    | X         |         | Involved in microbial recognition by upregulation of Toll-like receptors |
|        |          |                  |      |           | Possesses autocrine features [30, 129, 130] |
| IL-12  | IL-12    | X                | -    | -         | Predominantly produced by synovial Mφ and dendritic cells |
|        |          |                  |      |           | Promotes Th1 responses (reviewed in [62]) |
| IL-23  | X        | -                | -    |           | Predominantly produced by synovial Mφ and dendritic cells |
|        |          |                  |      |           | Shares p40 subunit with IL-12 and possibly antagonizes IL-12 [63] (reviewed in [62]) |
| IL-27  | X        | X                | X    | -         | Produced by Mφ  and its neutralization has anti-arthritis effects |
|        |          |                  |      |           | Possesses autocrine features [66] |
|        |          |                  |      |           | Pro-inflammatory role [67] |
| IL-17  | IL-17    | X                | -    | -         | Th0-Th1 lymphokine with pleiotropic, amplifying effects on Mφ in arthritis (reviewed in [24, 25]) |

IFN, interferon; LIF, leukemia inhibitory factor; Mφ, macrophages; RA, rheumatoid arthritis. Reproduced with permission from Kinne RW, Stuhlmüller B, Palombo-Kinne E, Burmester GR: The role of macrophages in rheumatoid arthritis. In Rheumatoid Arthritis. Edited by Firestein GS, Panayi GS, Wollheim FA. New York: Oxford University Press; 2006:55-75 [2].
Hormones
Females are affected by RA at a ratio of approximately 3:1 compared with males and experience clinical fluctuations during the menstrual cycle and pregnancy, indicating a major modulating role for sex hormones. Due to their expression of sex-hormone receptors and their cytokine response upon exposure to estrogens, monocytes/Mφ are strongly involved in hormone modulation of RA [33]. Indeed, physiological levels of estrogens stimulate RA Mφ to the production of the pro-inflammatory cytokine IL-1, whereas higher levels inhibit IL-1 production, conceivably mimicking the clinical improvement during pregnancy. Interestingly, selective estrogen receptor ligands inhibiting nuclear factor (NF)-κB transcriptional activity (but lacking estrogenic activity) can markedly inhibit joint swelling and destruction in experimental arthritis [34].

Cytokine stimuli with regulatory effects on macrophages
In addition to pro-inflammatory cytokines, several cytokines that regulate monocyte/Mφ function in RA have been described (summarized in the upper left quadrant of Figure 2). A systematic list of these cytokines is provided in Table 5. Interestingly, some of these molecules are produced by Mφ themselves (most notably, IL-10), so that autocrine regulation may also play a prominent role during the different clinical phases of RA. Other regulatory cytokines derive from other cell types present in the inflamed synovial membrane: T cells (for example, IL-4 and IL-13) or stromal cells (for example, IL-11). For these molecules, the reader is referred to recent publications or comprehensive reviews [25,35,36].

Monocyte/macrophage effector molecules in rheumatoid arthritis
Monocyte/macrophage effector molecules with proinflammatory effects in rheumatoid arthritis
Mφ produce a number of pro-inflammatory cytokines, as schematically shown in the upper right quadrant of Figure 2. A systematic list of the pro-inflammatory ILs is provided in Table 4.

Tumor necrosis factor-alpha receptors
TNF receptors are found in synovial tissue and fluid of patients with RA, especially in cases of severe disease [39]. There are two known TNF receptors, the R55 (TNF-R1) (high-affinity receptor) and the R75 (TNF-R2) (low-affinity receptor), which are expressed by both synovial Mφ and fibroblasts [47,48]. The two TNF receptors can operate independently of one another, cooperatively, or by ‘passing’ TNF-α to one another [37], a complexity that may explain the tremendous sensitivity of target cells (such as Mφ) to minute concentrations of TNF-α. TNF receptors can also be shed, binding to soluble TNF-α and hence acting as natural inhibitors in disease. Recent studies have demonstrated that TNF-R1 may be primarily responsible for pro-inflammatory effects of TNF-α, whereas TNF-R2 can be mediated by anti-inflammatory effects of TNF-α [48] (reviewed in [49]). Thus, selective blockade of TNF-R1, instead of broad blockade of all effects of TNF-α, may become an attractive therapeutic approach [48,50].

Interleukin-1
In the RA synovial membrane, IL-1 is found predominantly in CD14+ Mφ [51]; also, IL-1 levels in the synovial fluid significantly correlate with joint inflammation [52]. The two existing forms of IL-1 (IL-1α and IL-1β) show some differ-
ences (for example, low protein homology, stronger pro-
inflammatory regulation of the IL-1β promoter, and secretion of
inactive pro-IL-1β versus expression of membrane-bound IL-
α activity) but also strong similarities (that is, three-
dimensional structures of the essential domains, molecular
masses of pro-peptides, and mature-form processing protea-
ses), resulting in almost identical binding capacity to the IL-1
receptors and comparable function. In arthritis, IL-1 appears to
mediate a large part of the articular damage, as it profoundly
influences proteoglycan synthesis and degradation [43,53]. At
the same time, IL-1 induces the production of MMP-1 and
MMP-3 and enhances bone resorption; this is compatible with
recent evidence from arthritis models and human RA
suggesting that the tissue-destruction capacities of IL-1β may
outweigh its genuine role in joint inflammation [53].

Interleukin-1 receptors
The IL-1 type I receptor (IL-1R1), which mediates cell
activation via IL-1R accessory protein and IL-1 receptor-asso-
ciated kinase (IRAK), is found on numerous cells in the
synovial tissue of patients with RA [54]. In contrast, the type II
receptor (IL-1R2) (also found in soluble form in serum), which
lacks cell-activating properties and acts exclusively as a decoy
receptor, is low in synovial tissue [55]. Similarly, IL-1RA, a
soluble protein that blocks the action of IL-1 by binding to the
type I receptor without receptor activation, has been detected
only sporadically in RA synovial samples. In RA, the balance
between IL-1 and its physiological inhibitor IL-1RA is therefore
shifted in favor of IL-1, indicating a dysregulation crucial in
promoting chronicity [53]. However, therapeutic application of
IL-1RA (anakinra) appears to be only modestly effective in RA
(reviewed in [56]). Therefore, it remains to be clarified whether
the IL-1 pathway is a less suitable therapeutic target than TNF-
α (for example, due to functional redundancy in the IL-1
receptor superfamily) or whether the biological molecule IL-
1RA is suboptimal for therapy.

Interleukin-15
IL-15, a cytokine of the IL-2 family with chemoattractant
properties for memory T cells, is produced by lining layer cells
Table 5
Overview of anti-inflammatory cytokines relevant to macrophage (dys)function in rheumatoid arthritis

| Anti-inflammatory | Dual | Autocrine | Main pathogenetic features |
|------------------|------|-----------|----------------------------|
| IL-1RA           | X    | -         | X Produced by differentiated Mø and upregulated by pro-inflammatory mediators, including IL-1 itself or granulocyte macrophage colony-stimulating factor Autocrine contribution to the termination of inflammatory reactions [54,55] (reviewed in [53,56]) |
| IL-4             | X    | -         | Strong regulator of Mø functions but virtually absent in synovial tissue [73,131-133] |
| IL-10            | X    | X         | Produced by synovial Mø Strong regulator of Mø functions but relatively deficient in RA Possesses autocrine features [73,74] |
| IL-11            | X    | X         | Regulator of Mø functions in a paracrine regulatory loop with synovial fibroblasts [36,134] |
| IL-13            | X    | X         | Selective regulator of Mø functions Improves experimental arthritis (reviewed in [2,91]) |
| IL-16            | X    | X         | Known as an anti-inflammatory molecule [135,136], IL-16 also has pro-inflammatory properties (that is, correlates with metalloprotease-9 levels, progression of joint destruction, and levels of other pro-inflammatory cytokines) [137,138]. |
| IFN-β            | X    | -         | Clear anti-inflammatory and anti-destructive effects in experimental arthritides Therapy attempts in human RA thus far have been unsuccessful [149]. |
| TGF-β            | X    | X         | X Produced by Mø [78-80] Main regulator of connective tissue remodelling Potent inducer of hyaluronan synthase 1 Induces synovial inflammation (reviewed in [80]) but also suppresses acute and chronic arthritis [81,82] Induces inflammation and cartilage degradation in a rabbit model [140] Possesses autocrine features MMP can affect TGF-β via shedding of latent TGF-β attached to decorin (disease-enhancing loop). |

IFN-β, interferon-beta; IL, interleukin; IL-1RA, interleukin-1 receptor antagonist; Mø, macrophage(s); RA, rheumatoid arthritis; TGF-β, transforming growth factor-beta. Reproduced with permission from Kinne RW, Stuhlmuller B, Palombo-Kinne E, Burmester GR: The role of macrophages in rheumatoid arthritis. In Rheumatoid Arthritis. Edited by Firestein GS, Panayi GS, Wollheim FA. New York: Oxford University Press; 2006:55-75 [2].
(including Mφ) and is increased in RA synovial fluid [57]. Notably, peripheral or synovial T cells stimulated with IL-15 induce Mφ to produce IL-1β, TNF-α, IL-8, and monocyte chemotactic protein-1 [21,57] but not the regulatory IL-10. Because IL-15 is also produced by Mφ themselves, this cytokine may (re)stimulate T cells, possibly self-perpetuating a pro-inflammatory loop [57]. The expression of IL-15 in the RA synovial membrane, its biological function, and its successful targeting in experimental arthritis have generated large expectations on the use of a fully humanized anti-IL-15 antibody in clinical trials [56-58].

**Interleukin-18**

In the RA synovial membrane, this cytokine of the IL-1 family is expressed in CD68+ Mφ contained in lymphoid aggregates. CD14+ Mφ of the RA synovial fluid also express the IL-18 receptor [59]. The pro-inflammatory role of IL-18 in arthritis (and its potential suitability as a therapeutic target in RA) is indicated by the following findings: (a) IL-18 treatment markedly aggravates experimental arthritis [59], (b) intra-articular overexpression of IL-18 induces experimental arthritis, (c) IL-18 is involved in the development of experimental streptococcal arthritis (a strongly Mφ-dependent model), (d) IL-18 is selectively overexpressed in the bone marrow of patients with juvenile idiopathic arthritis and Mφ activation syndrome [5], (e) IL-18 can stimulate osteoclast formation through upregulation of RANKL (receptor activator of NF-κB ligand) production by T cells in RA synovitis, and (f) IL-18 mediates its action via classic induction of TNF-α, GM-CSF, and interferon (IFN)-γ [59] or functional Toll-like receptors TLR-2 and TLR-4 in synovial cells [30] or else through the induction of synovial acute-phase serum amyloid proteins. The clinical relevance of synovial IL-18 is emphasised by its correlation with the systemic levels of C-reactive protein (CRP); also, IL-18 and CRP decrease in parallel in synovial tissue and serum following effective treatment with disease-modifying anti-rheumatic drugs [60]. In addition, peripheral blood mononuclear cells of RA patients show low levels of the IL-18 binding protein (a natural inhibitor of IL-18) and reduced sensitivity to stimulation with IL-12/IL-18, indicating profound dysregulation of the IL-18 system [61].

**Interleukin-23**

The genuine role of IL-23, a cytokine of the IL-12 family predominantly produced by Mφ or dendritic cells, is unclear due to the sharing of the p40 subunit with IL-12 [62]. IL-23 has prominent pro-inflammatory functions, since transgenic expression in mice leads to multi-organ inflammation and premature death. IL-23 promotes various T-cell responses potentially relevant to RA [62]. Recent studies in experimental arthritis have demonstrated that mice lacking only IL-12 (p35<sup>−/−</sup>) show exacerbated arthritis, whereas mice lacking only IL-23 (p19<sup>−/−</sup>) are completely protected from arthritis [63]. In addition, activation of Mφ derived from arthritis-susceptible rats is paradoxically associated with reduced levels of pro-inflammatory mediators but high expression of IL-23 (p19), whereas non-susceptible rats show the inverse phenotype. If these findings were transferable to human RA, IL-23 would have a pro-inflammatory role and IL-12 a protective one. At the present time, it is unclear whether these findings fit into the recently introduced M1/M2 paradigm of differential Mφ activation [64,65] and especially whether this paradigm can be exploited for a better understanding of the role of Mφ in RA.

**Interleukin-27**

IL-27, another cytokine of the IL-12 family, is expressed by monocytes/Mφ following common inflammatory stimuli and displays a variety of pro- and anti-inflammatory properties [66]. In support of a pro-inflammatory role in arthritis, neutralizing antibodies against IL-27p28 suppress experimental arthritis [67].

**Chemokines and chemokine receptors**

Chemokines (subdivided into the CXC, CC, C, and CX3C families) are small proteins specialized in differential recruitment of leukocyte populations via a number of transmembrane receptors. Chemokines not only favor monocyte influx into inflamed tissue, but also play a key role in activation, functional polarization, and homing of patrolling monocytes/Mφ [65]. Notably, monocytes/Mφ express only select types of the numerous chemokine receptors (for example, CCRI, 2, 5, 7, and 8 as well as CX3CRI), representing a partially specific basis for prominent trafficking of monocyte/Mφ in arthritis. In RA, synovial Mφ produce several chemokines (for example, CCL3 [or Mφ inflammatory protein 1α], CCL5 [or RANTES], and CX3CL1 [or fractalkine]) and at the same time carry chemokine receptors, indicating the presence of autocrine loops in disease (reviewed in [68]). At the same time, chemokines are upregulated by the Mφ-derived TNF-α and IL-1. Significantly, some chemokines expressed in synovial Mφ (for example, IL-8 and fractalkine) are powerful promoters of angiogenesis, thus providing a link between Mφ activation and the prominent neo-vascularization of the RA synovium [69]. In RA, angiogenesis may be further promoted via activation of Mφ by advanced glycation end products, whereas thrombospordin-2 seems to downregulate angiogenesis. Because the enlargement of the vascular bed potentiates the influx of activated monocytes, down-modulation of the chemokine system represents a multi-potential target of anti-rheumatic therapy, as indicated by the promising results of treatment with a CCRI antagonist in RA [68].

**Macrophage migration inhibitory factor**

One of the first ILs ever discovered, migration inhibitory factor (MIF), is an early-response cytokine abundantly released by Mφ. MIF stimulates a number of Mφ functions in an autocrine fashion (for example, secretion of TNF-α, phagocytosis, and generation of reactive oxygen species [ROS]). In addition, MIF confers resistance to apoptosis in Mφ and synovial fibroblasts, thus prolonging the survival of activated, disease-
relevant cells. In RA, MIF is overexpressed in serum and synovial tissue in correlation with disease activity. Also, polymorphisms in the promoter or coding region of the human MIF gene are associated with features of juvenile idiopathic arthritis or adult RA [70].

Monocyte/macrophage effector molecules with anti-inflammatory/regulatory effects in rheumatoid arthritis

Mφ also produce anti-inflammatory cytokines, most notably IL-RA and IL-10, both cytokines engaged in autocrine regulatory loops (shown in the lower right quadrant of Figure 2) (Table 5).

Interleukin-1 receptor antagonist

Differentiated Mφ constitutively express IL-1RA, which is upregulated by pro-inflammatory mediators, including IL-1 itself or GM-CSF, and induces strong anti-inflammatory effects. By means of this feedback mechanism, Mφ therefore contribute to the termination of inflammatory reactions (reviewed in [71,72]) (see above).

Interleukin-10

IL-10, a Th2- and Mφ-derived cytokine with clear autocrine functions, reduces HLA-DR expression and antigen presentation in monocytes and inhibits the production of pro-inflammatory cytokines, GM-CSF, and Fc-γ receptors by synovial Mφ. Consistently with cytokine and chemokine downregulation, IL-10 clearly suppresses experimental arthritis. In spite of IL-10 elevation in serum and synovial compartments of patients with RA [73], some studies suggest a relative deficiency of IL-10 [74]. A combined IL-4/IL-10 deficiency probably tilts the cytokine balance to a pro-inflammatory predominance. In addition, the ex vivo production of IL-10 by RA peripheral blood mononuclear cells is negatively correlated with radiographic joint damage and progression of joint damage, suggesting that high IL-10 production is protective in RA. Similarly to IL-4, however, treatment with recombinant IL-10 does not improve RA. This may be partially explained by upregulation of the pro-inflammatory Fc-γ receptors I and II A on monocytes/Mφ (reviewed in [2]).

Monocyte/macrophage effector molecules with dual effects in rheumatoid arthritis

Cytokines with a dual role are indicated in Tables 4 and 5.

Interleukin-6

IL-6 is the most strikingly elevated cytokine in RA, especially in the synovial fluid during acute disease [75]. The acute rise is consistent with the role of IL-6 in acute-phase responses (Table 1). However, while IL-6 levels in the synovial fluid correlate with the degree of radiological joint damage, and IL-6 and soluble IL-6 receptors promote the generation of osteoclasts, this cytokine has phase-dependent effects; for example, it protects cartilage in acute disease but promotes excessive bone formation in chronic disease. While IL-6 is mostly produced by synovial fibroblasts and only partially by Mφ, two findings suggest that the striking IL-6 rise is a prominent outcome of Mφ activation: (a) the morphological vicinity of IL-6-expressing fibroblasts with CD14+ Mφ in the RA synovial tissue (reviewed in [2]) and (b) co-culture studies showing that IL-1 stimulates IL-6 production [17]. The role of IL-6 in experimental arthritis and the anti-arthritic effects of anti-IL-6 receptor antibodies suggest a role for anti-IL-6 therapy in RA [76] (reviewed in [77]).

Transforming growth factor-beta

In RA, Mφ express different transforming growth factor-beta (TGF-β) molecules and TGF-β receptors in the lining and sublining layers, at the cartilage-pannus junction, and in the synovial fluid [78-80]. The pro-inflammatory effects of TGF-β are substantiated by induction of Mφ expression of Fc-γ receptor III (which elicits the release of tissue-damaging ROS) and promotion of monocyte adhesion and infiltration during chronic disease (reviewed in [80]). At the same time, TGF-β has anti-inflammatory properties; for example, it counteracts some IL-1 effects, including phagocytosis of collagen and possibly MMP production. A protective role of TGF-β in RA is also suggested by the association between TGF-β polymorphism and disease severity; that is, alleles associated with low TGF-β expression are correlated with stronger inflammation and poorer outcome [81]. Likewise, experimental arthritis is significantly ameliorated by activation of TGF-β via adenoviral expression of thrombospondin-1 [82]. The effects of TGF-β on tissue inhibitor of MMP (TIMP) are also unclear, as the regulation of MMP and TIMP may depend on different tissue domains (superficial versus deep cartilage layers) and may vary for intra- or extracellular digestion of collagen (reviewed in [2]).

Treatment of human rheumatoid arthritis with conventional anti-macrophage approaches

The role of Mφ-derived cytokines in the perpetuation of RA, the pathophysiological dichotomy between joint inflammation and cartilage destruction, and the crucial significance of activated synovial Mφ in relation to permanent joint damage [1] have led to a radical re-evaluation of the conventional anti-inflammatory and disease-modifying treatments in relation to Mφ parameters in order to potentiate therapeutic effects (for example, via combination approaches [83]) and reduce side effects. For anti-Mφ effects of conventional anti-rheumatic therapy in RA (including methotrexate, leflunomide, anti-malarials, gold compounds, corticosteroids, and non-steroidal anti-inflammatory drugs), the reader is referred to a recent comprehensive review [11]. Recent findings show that conventional and specific anti-rheumatic treatments predominantly target sublining rather than lining Mφ; also, different therapeutic approaches seem to result in similar histological changes in the inflamed synovial membrane, including significant reduction of sublining Mφ. This, in turn, is significantly correlated with the degree of clinical improvement [11,12]. Thus, different pathogenetic mechanisms may funnel into
similar disease pathway(s), leading to massive activation of Mφ and providing the rationale for targeted anti-Mφ therapy.

Non-conventional and experimental anti-macrophage therapy

Counteraction of monocyte/macrophage activation at a cellular level

Apoptosis-inducing agents
Physical elimination of disease-relevant cells (for example, activated Mφ or osteoclasts) by apoptosis is advantageous because it circumvents secondary tissue damage by restraining cellular organelles in apoptotic vesicles. Phagocytic incorporation of liposome-encapsulated non-amino-bisphosphonates by activated monocytes, for example, induces apoptosis in these cells [84] (Figure 3). Systemic application of encapsulated bisphosphonates in experimental arthritis not only counteracts joint swelling, but also prevents local joint destruction and subchondral bone damage [85]; in addition, it shows protective effects on remote bone damage. Studies in RA show that a single intra-articular administration of clodronate liposomes leads to Mφ depletion and decreased expression of adhesion molecules in the lining layer of RA synovial tissue [86]. Selective targeting of activated Mφ has also been demonstrated using either apoptosis-inducing immunotoxins coupled to anti-Fc-γ receptor I (CD64) antibodies or folate receptor-mediated targeting (reviewed in [2]). In general, liposome encapsulation can also be exploited for selective delivery of Mφ-modulating drugs (e.g., IFN-β, IL-10).

Control of gene transcription
The transcription of most cytokine genes in monocytes/Mφ depends on the activation of NF-κB and NF-κM transcription factors or that of the activator protein-1 (AP-1) complex. In RA synovial Mφ, the expression of NF-κB is more pronounced than that of AP-1, a selectivity that may bear important therapeutic implications [89]. Accordingly, the anti-arthritic effects of IL-4 may be based on the selective suppression of NF-κB in Mφ. IL-10 also downregulates the production of pro-inflammatory monokines, inhibiting the nuclear factors NF-κB,
AP-1, or NF-IL-6. Unlike IL-4, IL-10 can also enhance degradation of the mRNA for IL-1 and TNF-α [reviewed in (2)]. In general, therefore, targeted inhibition of pro-inflammatory signal transduction pathways in Mφ represents an attractive therapeutic approach [90].

**Gene therapy in experimental arthritis**

Gene therapy has been applied in experimental arthritis models to counteract Mφ-derived IL-1 and TNF-α or to deliver/overexpress protective IL-1RA, soluble IL-1 type I receptor-IGG fusion protein, and type I soluble TNF-α receptor-IGG fusion protein. This has been extended to (Mφ-derived) anti-inflammatory cytokines (that is, IL-4, IL-10, IL-13, IFN-β, or TGF-β) and to ‘molecular synovectomy’ (either by expression of herpes simplex virus-thymidine kinase with subsequent administration of ganciclovir or by overexpression of Fas-ligand/inhibitors of nuclear translocation of NF-κB, resulting in synovial cell apoptosis [88,91,92]). Therefore, gene therapy aimed at neutralizing pro-inflammatory Mφ products, overexpressing Mφ-regulating mediators, or simply eliminating overly activated Mφ remains promising for the treatment of arthritis.

**Conclusion**

The multitude and abundance of Mφ-derived mediators in RA and their paracrine and autocrine effects (including those directed to other cells of the myeloid lineage) indicate that Mφ are local and systemic amplifiers of disease severity and perpetuation. The local mechanisms include (a) self-perpetuating chemokine-mediated recruitment of inflammatory cells, (b) cytokine-mediated activation of newly immigrated inflammatory cells, (c) cell contact-mediated activation of neighboring inflammatory cells, (d) cytokine- and cell contact-mediated secretion of matrix-degrading enzymes, (e) activation of mature dendritic cells and cytokine-mediated differentiation of Mφ (and possibly B cells, T cells, and mesenchymal cells) into antigen-presenting cells, with possible effects on spreading of autoimmune to cryptic epitopes, (f) neo-vascularization, with potentiation of cellular and exudatory mechanisms, and (g) (trans)differentiation of Mφ into osteoclasts involved in subchondral bone damage. At a systemic level, amplification of disease can proceed at least through the following mechanisms: (a) acute-phase response network, (b) systemic production of TNF-α, (c) anomalies in bone marrow differentiation, and (d) chronic activation of circulating monocytes.

Although uncovering the etiology of disease remains the ultimate goal of research, the efforts in understanding how activated Mφ influence disease have led to optimization strategies to selectively target activated Mφ in RA (Figure 3). This approach has at least two advantages: (a) striking the very cell population that mediates/amplifies most of the irreversible cartilage destruction and (b) minimizing adverse effects on other cells that may have no (or marginal) effects on joint damage.

**Competing interests**

The authors declare that they have no competing interests.

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**References**

1. Multerin D, Fitzgerald O, Bresnihan B: Synovial tissue macrophage populations and articular damage in rheumatoid arthritis. *Arthritis Rheum* 1996, 39:115-124.
2. Kinne RW, Stuhlmueller B, Palombo-Kinne E, Burmester GR: The role of macrophages in rheumatoid arthritis. In *Rheumatoid arthritis*. Edited by Firestein GS, Panayi GS, Wollheim FA. New York: Oxford University Press; 2006:55-75.
3. Smolen JS, Steiner G: Therapeutic strategies for rheumatoid arthritis. *Nat Rev Drug Discov* 2003, 2:473-488.
4. Stuhlmiiller B, Ungethuem U, Scholze S, Martinez L, Backhaus M, Kraetsch HG, Kinne RW, Burmester GR: Identification of known and novel genes in activated monocytes from patients with rheumatoid arthritis. *Arthritis Rheum* 2000, 43:775-790.
5. Maemo N, Takei S, Imanaka H, Yamamoto K, Kunitski K, Kawano Y, Oda H: Increased interleukin-18 expression in bone marrow of a patient with systemic juvenile idiopathic arthritis and unrecognized macrophage-activation syndrome. *Arthritis Rheum* 2004, 50:1935-1938.
6. Lavago L, Gunella G, Bardelli C, Spina S, Freeu LG, Viano I, Brunelleschi S: Anti-inflammatory drugs and tumor necrosis factor-alpha production from monocytes: role of transcription factor NF-kappaB and implication for rheumatoid arthritis therapy. *Eur J Pharmacol* 2004, 501:199-208.
7. Feldmann M, Brennan FM, Foxwell BM, Taylor PC, Williams RO, Maini RN: Anti-TNF therapy: where have we got to in 2005? *J Autoimmun* 2005, 25 Suppl:26-28.
8. van Rooijen N, Kesteren-Hendrikx E: ‘In vivo’ depletion of macrophages by liposome-mediated ‘suicide’. *Methods Enzymol* 2003, 373:3-16.
9. Sweeney SE, Firestein GS: Signal transduction in rheumatoid arthritis. *Curr Opin Rheumatol* 2004, 16:231-237.
10. Westra J, Doornbos-van der Meer B, de Boer P, van Leeuwen MA, van Rijswijk MH, Limburg PC: Strong inhibition of TNF-alpha production and inhibition of IL-8 and COX-2 mRNA expression in monocyte-derived macrophages by RWJ 67657, a 3 p8 mitogen-activated protein kinase (MAPK) inhibitor. *Arthritis Res Ther* 2004, 6:R384-R392.
11. Franz JK, Burmester GR: The needle and the damage done. *Ann Rheum Dis* 2005, 64:989-900.
12. Haringman JJ, Gerlag DM, Zwinderman AH, Smeets TJ, Kraan MC, Baeten D, Mclnnes IB, Bresnihan B, Tak PP: Synovial tissue macrophages: a sensitive biomarker for response to treatment in patients with rheumatoid arthritis. *Ann Rheum Dis* 2005, 64:834-838.
nuclear factor-kB transcriptional activity in models of rheumatoid arthritis. Arthritis Res Ther 2005, 7:R427-R438.

35. Taylor PC: Anti-cytokines and cytokines in the treatment of rheumatoid arthritis. Clin Exp Rheumatol 2005, 23:S39-S42.

36. Wong FK, Cucchielli IK, Robb L, Wicks IP: Endogenous IL-11 is pro-inflammatory in acute methylated bovine serum albumin/interleukin-1-induced (mBSA/IL-1) arthritis. Cytokine 2005, 29:72-76.

37. Garel M, Douni E, Wajant H, Löhden M, Clauss M, Maxeiner B, Georgopoulos S, Lesslauer W, Kollias G, Pfizenmaier K, et al.: The transmembrane form of tumor necrosis factor is the prime activating ligand of the 80 kDa tumor necrosis factor receptor. Cell 1995, 83:793-802.

38. Chomarat P, Kouloussis S, Plott A, Le Gars T: Transmembrane TNF is sufficient to induce localized tissue toxicity and chronic inflammatory arthritis in transgenic mice. J Immunol 1996, 46:86-97.

39. Feldmann M, Brennan FM, Maini RN: Role of cytokines in rheumatoid arthritis. Ann Rev Immunol 1996, 14:397-440.

40. 2006, 8:R153.

41. Klimiuk PA, Goronzy JJ, Björnsson J, Beckenbaugh RD, Weyand CM: Tissue cytokine patterns distinguish variants of rheumatoid synovitis. Arthritis Rheum 1999, 40:2109-2118.

42. Lequerré T, Gauthier-Jauneau AC, Bansard C, Derambure C, Hiron M, Vittecoq O, Daveau M, Mejidad O, Daragon A, Tron F, et al.: Gene profiling in white blood cells predicts infliximab responsiveness in rheumatoid arthritis. Arthritis Res Ther 2006, 8:R120.

43. Alsalameh S, Winter K, Al-Ward R, Wendler J, Kalden JR, Kinne RW: Distribution of TNF-alpha, TNF-R55 and TNF-R75 in the rheumatoid synovial membrane: TNF receptors are localized preferentially in the lining layer; TNF-alpha is distributed mainly in the vicinity of TNF receptors in the deeper layers. Scand J Immunol 1999, 49:278-285.

44. Kunisch E, Gandesiri M, Fuhrmann R, Roth A, Winter K, Kinne RW: Predominant activation of MAP kinases and pro-destructive/pro-inflammatory features by TNF-alpha in early-passage synovial fibroblasts via tumor necrosis factor receptor-1: failure of p38 inhibition to suppress matrix metalloproteinase-1 in rheumatoid arthritis. Ann Rheum Dis 2007, 66:1043-1051.

45. Alsalameh S, Amin RJ, Kunisch E, Jasim HE, Kinne RW: Preferential induction of prodestructive matrix metalloproteinase-1 and profibrotic interleukin-6 and progestin and E2 in rheumatoid arthritis synovial fibroblasts via tumor necrosis factor receptor-55. J Rheumatol 2003, 30:1680-1690.

46. Deng GM, Zheng L, Chan PK, Lenardo M: Amelioration of inflammatory arthritis by targeting the pre-rodent assembly domain of tumor necrosis factor receptors. Nat Med 2005, 11:1066-1072.

47. Wood NC, Dickens E, Symons JA, Duff GW: In situ hybridization of interleukin-1 in CD14+ positive cells in rheumatoid arthritis synovium. Cytom Part A 2002, 48:27-30.

48. Arend WP, Malvák M, Guthridge JC, Gabay C: Interleukin-1 receptor antagonist: role in biology. Ann Rev Immunol 1998, 16:27-55.

49. Dinarello CA: The IL-1 family and inflammatory diseases. Clin Exp Rheumatol 2002, 20:S13-19.

50. Deleuran BW, Chu CQ, Field M, Brennan FM, Katsikis P, Feldmann M, Maini RN: Localisation of interleukin-1 alpha, type 1 interleukin-1 receptor and interleukin-1 receptor antagonist in the synovial membrane and cartilage/pannus junction in rheumatoid arthritis. Br J Rheumatol 1992, 31:801-809.
101. Van Roon JA, Bijlsma JW, van De Winkel JG, Lafeber FP: Depletion of synovial macrophages in rheumatoid arthritis by an anti-Fc(\gamma)RI-Calicheamicin immunoconjugate. *Ann Rheum Dis* 2005, 64:865-870.

102. Wijnholds S, van De Winkel JG, Jacobs KM, Bijlsma JW, Lafeber FP, Van Roon JA: A shift in the balance of inhibitory and activating Fc\(\gamma\)R-I receptors on macrophages toward the inhibitory Fc\(\gamma\)R-I receptor \(\alpha\) is associated with prevention of B-lymphocyte activation in rheumatoid arthritis. *Arthritis Rheum* 2004, 50:3878-3887.

103. Liu H, Pope RM: Phagocytes: mechanisms of inflammation and tissue destruction. *Rheum Dis Clin North Am* 2004, 30:19-39.

104. Dao DN, Kremer L, Guerardel Y, Molano A, Jacobs WR Jr., Poroid synovial membrane. *Arthritis Rheum* 2004, 50:190-192.

105. Bouche G, Girard JP: The newest interleukins: recent developments. *Nat Immunol* 2004, 5:391-403.

106. Mogensen TH, Paludan SR: Reading the viral signature by Toll-like receptors and other pattern recognition receptors. *J Mol Med* 2005, 83:89-96.

107. Ilescu S: Rheumatic aspects of acquired immunodeficiency syndrome. *Curr Opin Rheumatol* 1996, 8:346-353.

108. Cheevers WP, Sneika KR, Trujillo JD, Emiryan R, Virology 2003, 306:116-125.

109. Iguchi T, Kurosaka M, Ziff M: Electron microscopic study of HLA-DR and monocyte/macrophage staining cells in the rheumatoid synovial membrane. *Arthritis Rheum* 1986, 29:600-613.

110. Bresnihan B, Gogarty M, Fitzgerald O, Dayer JM, Burger D: Apolipoprotein A-I infiltration in rheumatoid arthritis synovial tissue: a control mechanism of cytokine production? *Arthritis Res Ther* 2004, 6:R66.

111. Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK, Zuurawski G, Mosherf M, Qin J, Li X, et al.: IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity* 2005, 23:479-490.

112. Chen Q, Carroll HP, Gadina M: The newest interleukins: recent additions to the ever-growing cytokine family. *Vitam Horm* 2006, 74:207-228.

113. Carriere V, Roussel L, Ortega N, Lacombe DA, Ameur L, Aguilar L, Lestroy M, Potier MC, Haspeslagh C, Bell A, Rooney M: Polymorphisms in the interferon-gamma/interleukin-26 gene region contribute to sex bias in susceptibility to rheumatoid arthritis. *Arthritis Rheum* 2003, 48:2773-2778.

114. Radstake TR, Roelofs MF, Jenniskens YM, Oppers-Walgreen B, van Riel PL, Barreras P, Joosten LA, van den Berg WB: Expression of toll-like receptors 2 and 4 in rheumatoid synovial tissue and regulation by proinflammatory cytokines IL-12 and interleukin-18 via interferon-gamma. *Arthritis Rheum* 2004, 50:3885-3886.

115. Blaschke S, Schulz H, Schwarz G, Blaschke V, Muller GA, Reuss-Borst M: Interleukin-16 as an anti-inflammatory cytokine and inducer of TNFalpha. *Proc Natl Acad Sci U S A* 2002, 99:13444-13451.

116. Blaschke S, Schulz H, Schwarz G, Blaschke V, Muller GA, Reuss-Borst M: Correlation of circulating interleukin-16 with proinflammatory cytokines in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2001, 40:474-475.

117. Blaschke S, Schulz H, Schwarz G, Blaschke V, Muller GA, Reuss-Borst M: Enhanced concentrations of interleukin 16 are associated with joint destruction in patients with rheumatoid arthritis. *Rheumatol Int* 2004, 31:35-39.

118. Katz PK: IFN-beta in rheumatoid arthritis. *Franci Biosci* 2004, 9:3242-3247.

119. Blaschke S, Schulz H, Schwarz G, Blaschke V, Muller GA, Reuss-Borst M: Interleukin-16 expression in relation to disease activity in rheumatoid arthritis. *J Rheumatol* 2001, 28:12-21.

120. McGlade J, Franke S, Kentsch-Engel R, Oelzner P, Hein G, Stein K: Interleukin-16 expression in rheumatoid arthritis synovial tissue and regulation by proinflammatory cytokines IL-12 and interleukin-18 via interferon-gamma. *Arthritis Rheum* 2003, 174:1932-1937.

121. Bresnihan B, Gogarty M, Fitzgerald O, Dayer JM, Burger D: Apolipoprotein A-I infiltration in rheumatoid arthritis synovial tissue: a control mechanism of cytokine production? *Arthritis Res Ther* 2004, 6:R66.

122. Carriere V, Roussel L, Ortega N, Lacombe DA, Ameur L, Aguilar L, Lestroy M, Potier MC, Haspeslagh C, Bell A, Rooney M: Polymorphisms in the interferon-gamma/interleukin-26 gene region contribute to sex bias in susceptibility to rheumatoid arthritis. *Arthritis Rheum* 2003, 48:2773-2778.

123. Radstake TR, Roelofs MF, Jenniskens YM, Oppers-Walgreen B, van Riel PL, Barreras P, Joosten LA, van den Berg WB: Expression of toll-like receptors 2 and 4 in rheumatoid synovial tissue and regulation by proinflammatory cytokines IL-12 and interleukin-18 via interferon-gamma. *Arthritis Rheum* 2004, 50:3885-3886.

124. Henneman JA, Hall MA, Maini RN, Feldmann M, Brennan FM: Important immunoregulatory role of interleukin-11 in the inflammatory process in rheumatoid arthritis. *Arthritis Rheum* 1990, 33:1180-1187.

125. Allen JB, Wong HL, Costa GL, Bienkowski MJ, Wahl SM: Suppression of monocyte function and differential regulation of IL-1 and IL-1ra by IL-4 contribute to resolution of experimental arthritis. *J Immunol* 2000, 165:24-33.

126. Van Roon JA, Lafeber FP, Bijlsma JW: Synergistic activity of interleukin-4 and interleukin-10 in suppression of inflammation and joint destruction in rheumatoid arthritis. *Arthritis Rheum* 2001, 44:3-12.

127. Lard LR, Roep BO, Toes RE, Huizinga TW: Correlation of circulating interleukin-16 with proinflammatory cytokines in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2001, 40:474-475.

128. Blaschke S, Schulz H, Schwarz G, Blaschke V, Muller GA, Reuss-Borst M: Interleukin-16 expression in relation to disease activity in rheumatoid arthritis. *J Rheumatol* 2001, 28:12-21.

129. Klimpuk PA, Goronzy J, Weyand CM: IL-16 as an anti-inflammatory cytokine in rheumatoid synovitis. *J Immunol* 1999, 162:4293-4299.

130. Blaschke S, Schulz H, Schwarz G, Blaschke V, Muller GA, Reuss-Borst M: Interleukin-16 expression in relation to disease activity in rheumatoid arthritis. *J Rheumatol* 2001, 28:12-21.

131. Miller R, Franco S, Kentsch-Engel R, Oelzner P, Hein G, Stein K: Correlation of circulating interleukin 16 with proinflammatory cytokines in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2001, 40:474-475.