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## Cytokines in Rheumatoid Arthritis (RA)

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Selim Nalbant and Ahmet Merih Birlik

Additional information is available at the end of the chapter

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### Abstract

*Cytokines* are cell molecules that are secreted by immune cells and aid cell to cell communication in immune responses and stimulate the movement of cells towards sites of inflammation, infection and trauma. So, the cytokines are the main part of the immune network to provide the communication in rheumatoid arthritis (RA) too. In RA, cytokines may be classified into four groups: pro-inflammatory cytokines, inflammatory cytokines in joints, anti-inflammatory cytokines and natural cytokine antagonists. After the initial stimuli have occurred, cytokines play a role in communication between the parts of immune system in every step of the pathophysiology process of RA. The differentiation of naive T cells into Th17 cells results in inflammation (synovitis) in joints. B cells further the pathogenic process through antigen presentation and autoantibody and cytokine production. The release of cytokines, especially tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6 and IL-1, causes synovial inflammation. In addition to their articular effects, pro-inflammatory cytokines promote the development of systemic effects (anemia, cardiovascular disease, fatigue and depression). So, cytokines are the main molecules contributing to all facets of the disease.

**Keywords:** cytokines, effector cells, rheumatoid arthritis, anti-cytokine treatment

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### 1. Cytokine and rheumatoid arthritis

Rheumatoid arthritis (RA) is a progressive inflammatory disease, which is characterized by symmetrical polyarthritis. As an inflammatory disease, RA is characterized by increased levels in pro-inflammatory cytokines. In this complex cytokine environment, apart from arthritis, systemic manifestations also occur. Genetic and environmental factors are contributory to this complex nature of RA process. T cells, B cells and their cytokines play key roles in the pathophysiology of RA. Today's modern RA treatment basically targets these cytokines. While we do this, we are generally treat the "*normal and abnormal cytokine response*" at the same

time, because we do not know the main etiology of this abnormal cytokine response. To better manage RA, we should understand the role of cytokines and the relation between the effector cells [1–6].

The term “**cytokine**” is derived from a combination of two Greek words—“cyto” **meaning** cell and “kine” **meaning** move. **Cytokines** are cell molecules that are secreted by immune cells and aid cell to cell communication in cases of inflammation, infection and injury. So, the cytokines are vital part of the immune network to provide communication [7].

## 2. What is the origin of this complex cytokine response?

RA is an autoimmune disease. The term autoimmunity usually means a lot information that defines *the way* but not *the origin of the process*, and this stands for RA too. On the other hand, autoimmunity also means autoantibody production. In RA, there are two autoantibodies, rheumatoid factor and anti-cyclic citrullinated peptide antibodies, which contribute to inflammation. In the end, chronic inflammatory arthritis and the organ damage occur [8, 9].

The very early events of RA pathogenesis get into motion by breaking T-cell and/or B-cell tolerance and/or ignorance. However, this mechanism was poorly defined. After, shaping of this autoimmune background, some subsequent events intervene to perpetuate the process of synovial inflammation. What directs this process to the joints is unknown and it probably includes biomechanical factors, neuro-immuno-endocrinological interactions and altered articular microvascular microenvironment. Several factors have been proposed to have an association with the susceptibility and severity of rheumatoid arthritis [1–10].

These factors are as follows:

(1) Genetic loci:

- HLA-DR4 alleles
- *PTPN22* (protein tyrosine phosphatase, nonreceptor type 22)
- *PADI4* (peptidyl arginine deiminase, type IV)
- *CTLA4* (cytotoxic T-lymphocyte antigen 4)
- Fc $\gamma$ Rs (Fc receptors for IgG)
- Various cytokine and cytokine-receptor loci.

(2) Environmental factors (smoking, stress, hormonal factors, etc.)

(3) Infectious organisms

The earliest event in RA pathogenesis perhaps is activation of the innate immune response. In this first step, cytokines play a role in communication between the parts of immune system. In second step, antigen-presenting cells present arthritis-associated antigens to T cells. This step is the starting point of the cytokine effect, which augments the inflammation and

stimulate the other systems (such as lipid mediators, nitric oxide, RANKL-RANK signaling, etc.) that cause joint destruction and the organ damage [11–13].

### 3. How can we classify this cytokine network in RA

Actually to make classification of cytokines for rheumatoid arthritis is not feasible. Because many of them have some pleotropic effect at the same time. However, we may basically, classify cytokines four groups in the pathogenesis of rheumatoid arthritis. Actually, this classification is not a real one, it is just for the establishment of understanding the whole mechanism [10] (Table 1).

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#### 1. Pro-inflammatory cytokines: IL-1 and TNF-alpha cytokine role in

##### IL-1

- Increased synovial fibroblast cytokine, chemokine, MMP and PG release
- Increased monocyte cytokine, reactive oxygen intermediate and PG release
- Osteoclast activation
- Endothelial cell adhesion molecule expression
- Acute-phase protein production
- Cardiovascular disease promotion
- HPA axis dysregulation (fatigue and depression) [2, 14, 15]

##### TNF-alpha

- Increased monocyte activation, cytokine release, prostaglandin release
- T-cell clonal regulation
- Increased endothelial cell adhesion molecule expression, cytokine release
- Acute-phase protein production and fatigue-depression [2, 16]

#### 2. Inflammatory cytokines in joints: IL-1 and TNF-alpha, IL-6, IL-15, IL-16, IL-17, IL-18, IFN-gamma, granulocyte macrophage-colony stimulating factor

##### IL-6

- Osteoclast and B-cell activation
- T-cell proliferation and differentiation
- Acute-phase protein and hepcidin (anemia) production [17, 18]

##### IL-15

- Structural similarities to IL-2,4 produced primarily by macrophages
- Regulation of synovial inflammation [19–21]

##### IL-16

- Suppression of IFN- $\gamma$ , TNF- $\alpha$  and IL-1 $\beta$  expression
- Anti-inflammatory effect by regulation of Tregs [22]

#### **IL-17**

- Increase local chemokine production
- Augmentation of immune response (increase IL-6 production)
- Cartilage damage
- Promotes the effect of IL-1b, TNF-a and IFN-g [20, 23, 24]

#### **IL-18**

- Increase the production of pro-inflammatory cytokines, chemokines, adhesion molecules and RANKL which are the main molecules of joint destruction
- Increase the production of fibroblast-like synoviocytes and chondrocytes [25, 26]

#### **IL-21**

- Activate TH17 cells
- Induces osteoclastogenesis
- Plasma levels shows correlation with DAS28 [2]

#### **IFN-gamma**

- Immune modulation (both protection and activation) [27, 28]

#### **Granulocyte macrophage-colony stimulating factor (GM-CSF)**

- Promotes existing RA [29]

### **3. Anti-inflammatory cytokines**

#### **IL-10**

- Inhibit Th1 cell activity by suppressing IFN- $\gamma$  expression
- Direct inhibitory effect on the macrophage activity in the synovium
- Elevated levels in the synovial fluid
- Dominant suppressive cytokine effect
- Protection against cartilage destruction combination with IL-4 [2, 7]

#### **IL-4**

- Increased level in synovial fluid during only synovial inflammation
- Preventing collagen type I breakdown in RA [30–33]

#### **IL-13**

- Synergistic or inhibitory roles during the arthritis with IL-10, IL-21R, galectin-3 and TGF $\beta$  [34]

#### **IL-20**

- Regulates osteoclast differentiation [35]

### **4-Natural cytokine antagonists**

#### **IL-1 receptor antagonist (IL-1ra)**

- Low levels of IL-1 receptor antagonist (IL-1ra) causes erosive disease in patients and [36]

#### **Soluble type 2 IL-1 receptor**

- Cause competitive inhibition by binding interleukin-1 $\alpha$  (IL1A), interleukin-1 $\beta$  (IL1B) and interleukin 1 receptor antagonist (IL1Ra), and acts as a pseudo receptor activity that inhibits the activity of its ligands [37, 38]

#### **Soluble TNF receptor (sTNF-RI)**

- It is not well-known; possible effect is to cause cleavage of TNF alpha [39]

#### **IL-18 binding protein**

- Protect against the joint destructive effect by binding IL-18 in RA [40]

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**Table 1.** Actions of cytokines that play major roles in RA pathobiology.

### **3.1. Pro-inflammatory cytokines**

Interleukin (IL)-1 and tumor necrosis factor (TNF)-alpha are the main pro-inflammatory cytokines involved in RA. The influx and/or local activation of mononuclear cells and the formation of new blood vessels are main findings in synovial membrane. Differentiation of naive T cells into Th17 cells contributes to synovitis. B cells further the pathogenic process through antigen presentation and autoantibody and cytokine production. Enzymes secreted by synoviocytes and chondrocytes degrade cartilage. The release of cytokines, especially TNF-alpha and IL-1, have multiple detrimental effects on cartilage and bone. Pro-inflammatory cytokines act locally but also have systemic effects, such as production of acute-phase proteins, anemia of chronic disease, cardiovascular disease, osteoporosis, etc. [1–7, 11, 12].

### **3.2. Inflammatory cytokines in joints**

These cytokines are basically cytokine found in higher levels in the joints of patients with RA than in the serum. Most are pro-inflammatory cytokines. They cause mostly local joint destruction and also systemic effects of the disease and include IL-1, TNF-alpha, IL-6, IL-15, IL-16, IL-17, IL-18, interferon (IFN)- $\gamma$ , granulocyte macrophage-colony stimulating factor) [10–12].

### **3.3. Anti-inflammatory cytokines: (IL-4, IL-10, IL-11, IL-13 and IL-20)**

In case of an inflammatory state, such as RA, the immune system utilizes anti-inflammatory cytokines to restrict the inflammatory reaction. In RA synovitis, there is an imbalance between pro-inflammatory and anti-inflammatory cytokines due to insufficient local concentrations of anti-inflammatory cytokines, IL-10, IL-11 and IL-13 to mediate counter-regulatory activity against the dominant pro-inflammatory cytokines. This is almost valid for the T-cell-derived cytokines, which are IL-2 and IL-4. They are also absent, which may impair Treg-cell generation and favor TH1-cell or TH17-cell immune responses [1, 2, 10].

### **3.4. Natural cytokine antagonists**

Immune system is the most complex system, which has a self-limiting or self-controlling mechanism. The known molecules for this purpose are IL-1 receptor antagonist (IL-1ra),

soluble type 2 IL-1 receptor, soluble TNF receptor (sTNF-RI) and IL-18 binding protein. However, current information about them is not entirely known. It is suggested that TNFR1 and the type II IL-1R have a regulatory role in sequestering soluble TNF and IL-1 away from their cell-bound receptors. Their detected levels in synovial tissues and fluid are insufficient to counteract the inflammatory cytokines and bring cytokine homeostasis. We currently use these natural anti-inflammatory molecules for therapeutic reasons [1–6].

#### 4. Conclusion

As a result, cytokine effects do not occur with a single cytokine signalling cascade. There are many factors effecting the cytokine response. These are not only to control the equilibrium between inflammatory and anti-inflammatory cytokines but also the pleotropic and individual effects of cytokines. Here, we describe the topics of cytokine network only. It will be crucial to select cytokine targets based not on one single inflammatory pathway but rather on a bio-systematic approach to pathogenesis. Implicit in this will be the recognition of pivotal checkpoints that facilitate the progression from autoimmunity to chronic inflammation [1, 11–13].

As it was seen, cytokines are the main molecules at all these stages. However, they are not only the origin of the all cascade but also the last point which is occurring the damage. So, this fact makes the cytokine as a target molecule to treat.

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