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REVIEW ARTICLE

Role of Cytokines in Pathogenesis of Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis has multi factorial pathogenesis synovial hyperplasia and joint deformation is a striking characteristic of RA patients. The synovium thickens, and the joint becomes swollen and painful. In arthritis, macrophages accumulate in the synovial membrane and at the cartilage-pannus junction. Macrophages can be activated by several factors expressed in arthritic joint. Neutrophil normally function as a first line of defence against invading pathogens. In a joint affected by RA, neutrophils are the most abundant cellular infiltrators constituting about 90% of the cells found in synovial fluid. Cytokines are small, short-lived proteins that have a key role in integrating responses to a variety of stimuli in immune and inflammatory processes. Binding of their cognate receptors on target cells is followed by activation of enzymes involved in a variety of intracellular signalling cascades that ultimately modulate the genetic cellular response to the particular ligand.

Keywords: Rheumatoid arthritis, Neutrophils, Macrophages, Cytokines, Pannus Formation.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis has multi factorial pathogenesis synovial hyperplasia and joint deformation is a striking characteristic of RA patients. The synovium thickens, and the joint becomes swollen and painful. The normally hypo cellular synovium becomes infiltrated with immune cells (T cells, B cells, macrophages, and neutrophils). Mononuclear cells infiltrating the joint produce large quantities of pro-inflammatory cytokines that induce further synoviocytes activation and proliferation leading to pannus formation. *Pannus* is a hyperplasic membrane of synoviocytes that invades the tissues and targets the underlying bone and cartilage. Further production of matrix-degrading enzymes results in the loss of cartilage and the formation of osteoclasts. In RA, joint destruction is irreversible. Osteoclasts reabsorb bone, and cause release of proteolytic enzymes, such as metalloproteinase, aggrecanases, and Cathepsin. These in turn are responsible for further destruction of extracellular matrix constituents, including bone and cartilage proteoglycans. As a result of this, cartilage and bone lose their normal architecture and function, which leads to joint deformation, instability, pain, and severe inflammation. Also the synovial fluid, which is normally a cellular, becomes highly infiltrated with cells predominantly with neutrophils. All these changes result in reduced functioning of the joint accompanied by pain and stiffness (Goronzy & Weyand, 2009).

Cellular mechanism of rheumatoid arthritis

Macrophage:

Macrophages are the key participants in many inflammatory responses. They are professional antigen presenting cells activating T cells through antigen presentation and co-stimulatory molecules. In arthritis, macrophages accumulate in the synovial membrane and at the cartilage-pannus junction. Macrophages can be activated by several factors expressed in arthritic joint. For example, macrophages can be activated by the IFN-g produced by Th1 lymphocytes in RA joints (Hu, X *et al.*, 2002). Macrophage activation can also result from direct cell–cell contact with T cells. Activated macrophages in RA synovial tissue produce high levels of cytokines and chemokines, such as interleukin-1b (IL-1b), tumor necrosis factor-alpha (TNF-α), IL-6, IL-8, granulocyte or macrophage

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colony stimulating factor (GM-CSF), macrophage inflammatory protein 1a (MIP-1a), and monocytes chemo attractant protein-1 (MCP-1) (Feldmann, M. *et al*. 1996). Activated macrophages might accumulate by failing to turnover and subsequently produce a variety of pro-inflammatory cytokines and chemokines to promote development of arthritis and bone destruction (Deng & Lenardo, 2006).

T Cells:

T cells play an important role in the pathogenesis of rheumatoid arthritis. First, T cells are one of major cells in inflamed synovial membranes in RA. There are a large number of CD4+ T cells infiltrating into the synovial tissue of patients with RA (Matsuoka *et al*., 1991). Second, RANKL from activated CD4+ T cells in the arthritic joints exerts a pivotal role in bone destruction (Kong *et al*., 1999). Third, genetic studies demonstrate that RA is associated with a particular MHC class II antigen, HLA-DR4, which apparently presents antigenic peptides to T cells (Choy & Panayi, 2001). Lastly, CD4+ T cells are involved in the stimulation of non-T effectors cells to produce inflammatory cytokines such as TNF-α and IL-1.

B Cells:

In the pathogenesis of RA, B cells have been found to be involved in the production of auto antibodies such as RF, ACPA and anti-collagen II antibodies and, also contribute to the inflammatory response by producing cytokines, such as IL-6 and by serving as antigen-presenting cells (APCs) to activate T cells. Recently it has been demonstrated that collagen induced arthritis (CIA) could not be induced in mice deficient for B cells (Svensson *et al.*,1998) which affirms the role of B-cells in the pathogenesis of RA.

Neutrophils:

Neutrophil normally function as a first line of defense against invading pathogens. In a joint affected by RA, neutrophils are the most abundant cellular infiltrators constituting about 90% of the cells found in synovial fluid. These neutrophils expressing class II MHC molecules have recently been found to stimulate T-cell proliferation. Such an interaction between neutrophils and T cells could eventually prove important in the pathogenesis of RA. Besides, neutrophils produce high levels of ROS and enzymes such as matrix metalloproteinase (MMP or gelatinase B), LTB4 and a wide variety of cytokines, including IL-1β, IL-6 and TNF-α (Cascao *et al.,* 2010).

Synovial fibroblasts:

Normal synovial tissue consists of two anatomically distinct layers: a surface epithelial layer (synovial lining), and an underlying layer, including macrophage-like synoviocytes (MLS) and fibroblast-like synovial cells (FLS, also called synovial fibroblasts). One hallmark of RA is synovial hyperplasia. FLS hyperplasia has been shown to precede the accumulation of inflammatory cells, suggesting a key early role for FLS (Qu, *et al*., 1994). FLS mediate inflammation and autoimmunity through a wide range of mechanisms. FLS respond to, and themselves produce, inflammatory mediators including IL-1, IL-6 and TNF-a. They are also important mediators in initiation and development of arthritis. The abundance of FLS at the cartilage or pannus junction is consistent with a role for FLS in marginal cartilage erosion (Deng & Lenardo, 2006).

ROLE OF CYTOKINES IN PATHOGENESIS OF RHEUMATOID ARTHRITIS

Cytokines are small, short-lived proteins that have a key role in integrating responses to a variety of stimuli in immune and inflammatory processes. Binding of their cognate receptors on target cells is followed by activation of enzymes involved in a variety of intracellular signalling cascades that ultimately modulate the genetic cellular response to the particular ligand (Kokkonen *et al.,* 2010).

The most abundant cytokines promoting inflammatory responses are TNF-α, IL-1β and IL-6. TNF-α is considered to be a hallmark cytokine in the pathogenesis of RA. The importance of TNF-α was reflected by the spontaneous development of arthritis in TNF-α transgenic mice that over expresses a modified human TNF-α Tran's gene (Keffer *et al.,* 1991). TNF-α induces the production of other pro inflammatory cytokines, activates poly morphonuclear cells and enhances cartilage breakdown (Zwerina *et al.*,2005) and also regulates the expression of IL-1β (Petrovic-Rackov *et al.*,2006). Together IL-1β and TNF-α play an important role in the communication among the many cells in the rheumatoid joint. These cytokines up-regulate the expression of

CAMs on endothelial cells, thereby direct the emigration of blood cells from the circulation into the synovium (Proudman *et al.*, 1999). They also stimulate the production of chemokines, which provide important signals for the process of cell infiltration.IL-1β is considered to be key mediator with regard to cartilage and bone the destruction (Joosten *et al.*, 1999). IL-1β along with TNF-α stimulates synoviocytes and chondrocytes to release MMPs and other proteinase and also up-regulates the expression of pro-inflammatory genes, including cyclooxygenase-2 and nitric oxide synthase (Dayer *et al.*, 1986). IL-1β has been readily detected in serum of RA patients and its levels are found to correlate with disease severity (Eklund *et al.*, 2007). It has been observed that mice that are deficient for the IL-1β receptor antagonist, a naturally occurring counter regulatory cytokine, develop a spontaneous inflammatory arthritis (Horai *et al.*, 2008).

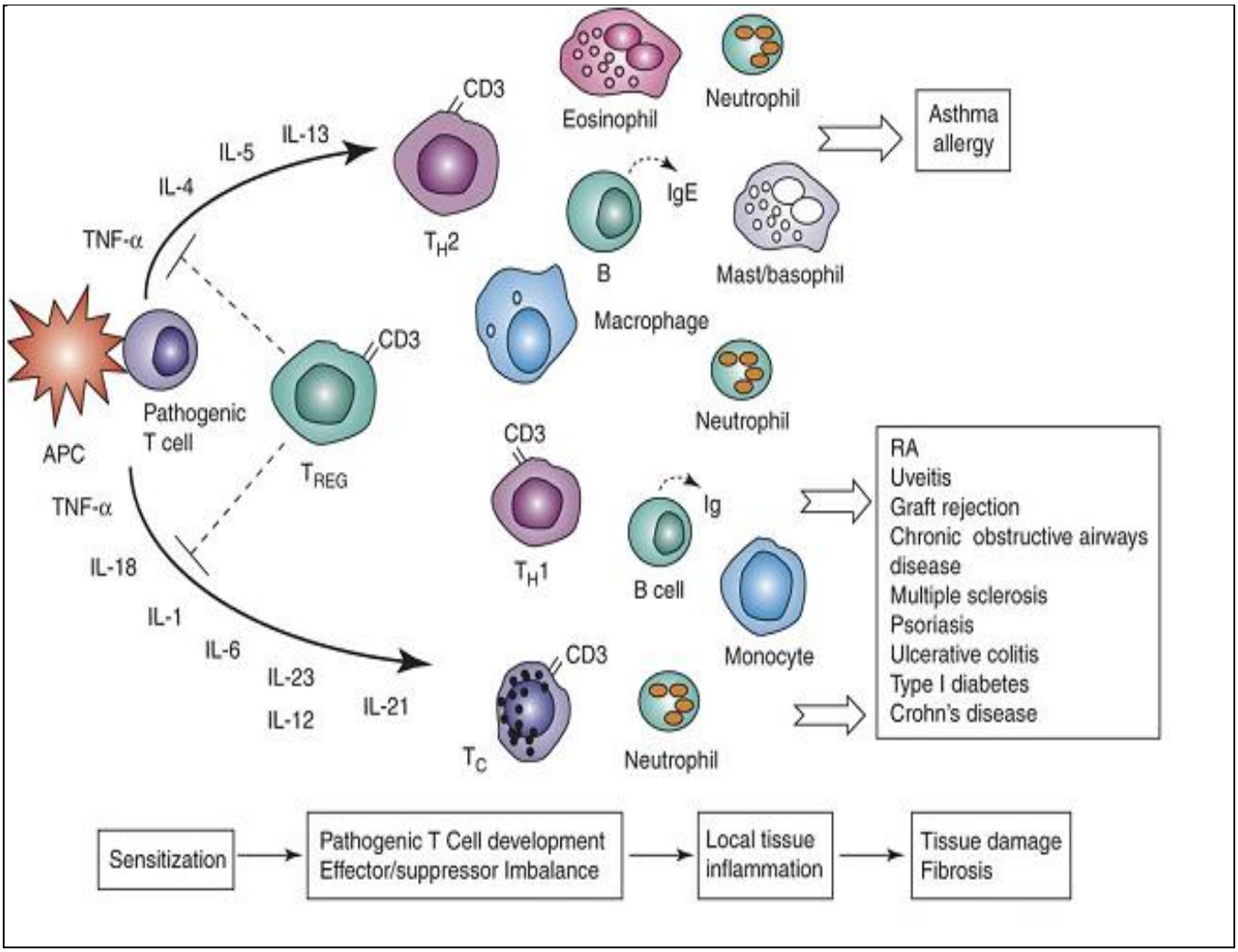

Figure No.1: Modulation of immune responses by cytokines (Taylor & Feldmann, 2004).

Interleukin (IL)-6 is a pleiotropic pro-inflammatory cytokine that induces osteoclasts differentiation and contributes for joint destruction in RA. IL-6 is found to act as a growth factor for T cells and also enhances B cell proliferation and subsequent antibody production (Gabay, 2006).

IL-4 is produced by activated CD4+ T cells and it promotes the maturation of Th2 cells and inhibits the differentiation of native T cells to Th1 cells. (Fiorentino *et al.*, 1989) IL-4 stimulates proliferation, differentiation or activation of several cell types, including fibroblasts, endothelium cells and epithelium cells (Chomarat *et al.*, 1997).

It is known to be a potent anti-inflammatory cytokine that acts by inhibiting the synthesis of pro inflammatory cytokines such as IL-1β, TNF-α, IL-6, IL-8 and IL-12 by macrophages and monocytes (El-Kady *et al.*, 2008). Moreover, IL-4 stimulates the synthesis of several cytokine inhibitors such as interleukin-1 receptor antagonist (IL-1Ra). In addition it exerts protective effect towards extracellular matrix degradation by suppressing metalloproteinase production and stimulating

the production of tissue inhibitor of metalloproteinase-1 in human mononuclear phagocytes (Cawston *et al.*, 1996)
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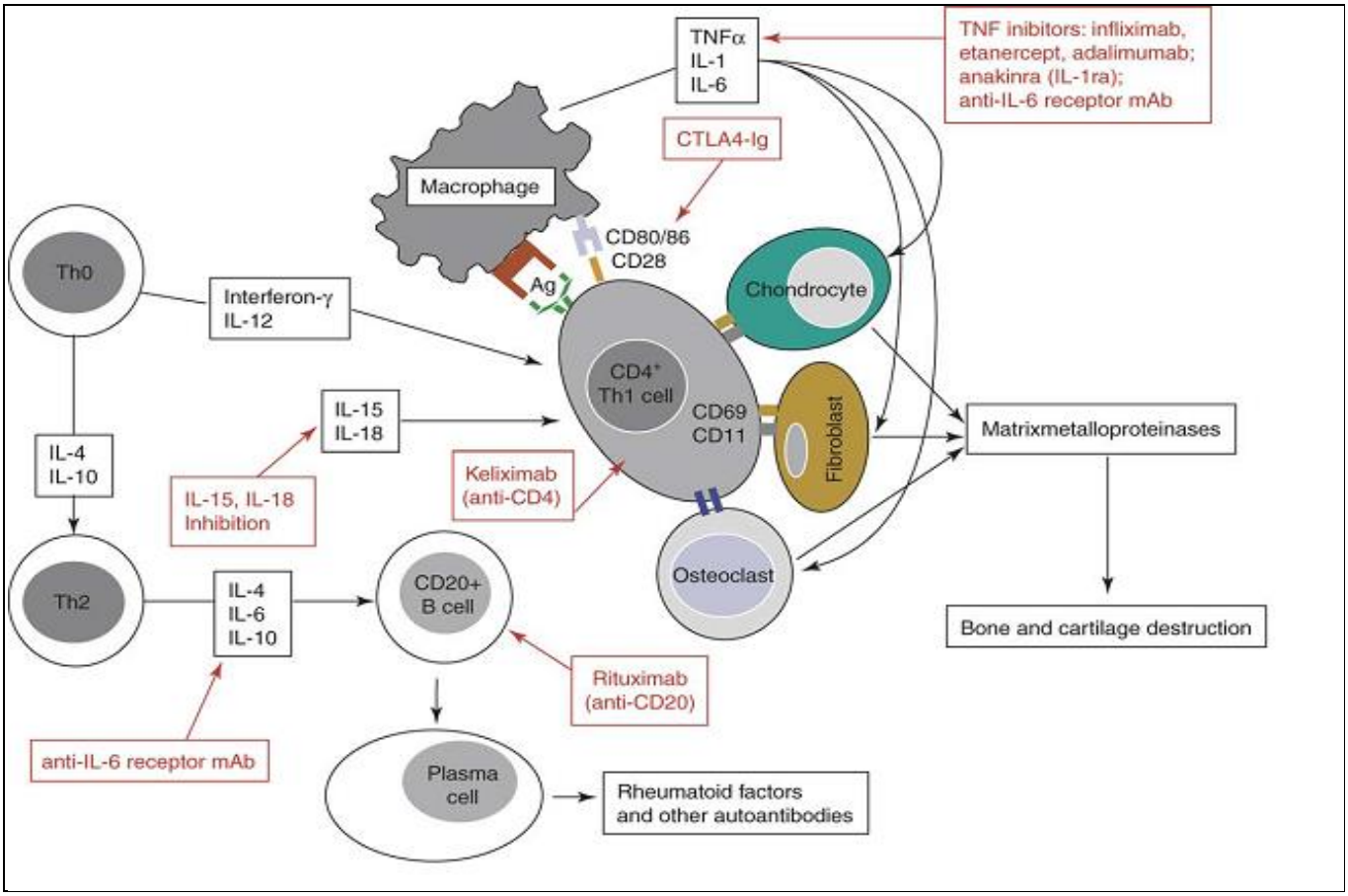

Figure No.2: Major cell types & role of cytokines in destruction of bone & cartilages (Taylor & Feldmann, 2004).

BIOLOGICAL MEDIATORS OF INFLAMMATION IN ARTHRITIS

A variety of biological mediators act in performance to commence and complete the inflammatory reaction in arthritis. The major biochemical mediators include cyclo-oxygenase (COX), Lipoxygenase (LOX), matrix metalloproteases (MMPs), nitric oxide synthases (NOS), tissue inhibitors of metalloproteases (TIMPs), prostaglandins (PG), leukotrienes (LT) and nitric oxide (NO). These mediators act via different interconnected pathways resulting in arthritic inflammation.

Cycloxygenase (COX)

Cycloxygenase (COX) is known to be a biosynthetic enzyme responsible for conversion of arachidonic acid (AA) to prostaglandins. COX converts arachidonic acid into prostaglandin H2 (PGH2), which is further catalyzed by distinct synthases into 5 major bioactive prostaglandins (PGE2, PGI2, PGF2 and PGD2) and thromboxane A2 (TXA2). Cycloxygenase basically has two isoforms; COX 1 and COX 2. It is well known that COX 1 is a housekeeping enzyme present in most cells and its expression is generally constitutive. In contrast, COX 2 is an inducible enzyme of cancer, inflammation. Its expression is low and undetectable in most cells but upon stimulation by cytokines, endotoxin, tumor promoters, growth factors etc. In case of osteoarthritis, COX-2 expression is induced in the cartilage and in rheumatoid arthritis it is induced in the synovial tissue (Amin *et al.*, 1997).

Lipoxygenase (LOX)

In mammals, LOX enzymes convert arachidonic acid to leukotrienes A4 (LTA4) which is then converted enzymatically to bioactive leukotrienes (LTs), LTB4, LTC4, LTD4 and LTE4. 5-LOX is especially known to play a vital role in the pathogenesis of RA. (Mathis *et al.*, 2007) LTB4 is considered as the most potent chemotactic agent and mediates the infiltration of leukocytes into the RA joint. It stimulates several leukocyte functions related to inflammation i.e. aggregation, release of

lysosomal enzymes and production of superoxide anion. In addition, it induces the formation of suppressive and cytotoxic T-lymphocytes (Peter-Golden *et al.*, 2008). LTB4 is also reported to induce the production and release of cytokines for example TNF-α and IL- 1β and also activates neutrophils to release superoxides and proteolytic enzymes, which in turn cause matrix destruction (Marcoullier *et al.*, 2005). In view of these properties, inhibitors of leukotrienes synthesis are thought to possess therapeutic potential for treatment of arthritic and inflammatory diseases (Ammon *et al.*, 1992).

Nitric oxide (NO)

Nitric oxide (NO) is a reactive free radical that has been implicated in tissue injury in rheumatoid arthritis. NO is a small molecule that is synthesized by a family of enzymes in mammalian cells during the conversion of L-arginine to L-citrulline. This reaction is catalyzed by one of three isoforms of nitric oxide synthase (NOS). Two of the NOS enzymes, namely endothelial NOS and neuronal NOS, constitutively produce relatively low levels of NO. It has been observed that levels of NO are elevated in serum and synovial fluid and the serum nitrite concentration is found to be correlated with disease activity or radiological progression in RA. Moreover, decreased production of NO via suppression of i-NOS has been reported to reduce the arthritic symptoms and also afford protection against the loss of body weight. This suggests that overproduction of NO is critical in the pathogenesis of RA (Nagy *et al.*, 2007).

REFERENCES

1. Amin, A.R., Attur, M., Patel, R.N., Thakker, G.D., Marshall, P.J., Rediske, J., Stuchin, S.A., Patel, I.R., Abramson, S.B., 1997. Super induction of cyclooxygenase-2 activity in human osteoarthritis-affected cartilage. Influence of nitric oxide. *The Journal of Clinical Investigation*, Vol. 99, pp. 1231-1237.
2. Ammon, H.P, Safayhi, H., Mack, T., Sabieraj, J., Anazodo, M.I., Subramanian, L.R., 1992. Boswellic acids: Novel, specific, non–redox inhibitors of Lipoxygenase. *Journal of Pharmacology and Experimental Therapeutics*, Vol. 261, Issue 3, pp.1143-1146.
3. Cascao, R., Rosario, H.S., Souto-Carneiro, M.M., Fonseca, J.E., 2010. Neutrophils in rheumatoid arthritis: More than simple final effectors. *Autoimmunity Reviews*, Vol. 9, Issue 8, pp. 531-535.
4. Cawston, T.E., Ellis, A.J., Bigg, H., Curry, V., Lean, E., Ward, D., 1996. Interleukin-4 blocks the release of collagen fragments from bovine nasal cartilage treated with cytokines. *Biochimica et Biophysica Acta*, Vol. 1314, Issue 3, pp. 226-232.
5. Chomarat, P. and Banchereau, J., 1997. An update on interleukin-4 and its receptor. *European Cytokine Network*, Vol. 8, Issue 4, pp. 333-344.
6. Choy, E.H. and Panayi, G.S., 2001. Cytokine pathways and joint inflammation in rheumatoid arthritis. *The New England Journal of Medicine*, Vol. 344, Issue 12, pp. 907–916.
7. Dayer, J.M., Rochemonteix, De, B., Burrus, B., Demczuk, S., Dinarello, C.A., 1986. Human recombinant interleukin 1 stimulates collagenase and prostaglandin E2 production by human synovial cells. *The Journal of Clinical Investigation*, Vol. 77, Issue 2, pp. 645-648.
8. Deng, G.M. and Lenardo, M., 2006. The role of immune cells and cytokines in the pathogenesis of rheumatoid arthritis. *Drug Discovery Today: Disease Mechanism*, Vol. 3, Issue2, pp. 163-168.
9. Deng, G.M. and Lenardo, M., 2006. The role of immune cells and cytokines in the pathogenesis of rheumatoid arthritis. *Drug Discovery Today: Disease Mechanism*, Vol. 3, Issue2, pp. 163-168.
10. Eklund, K.K., Leirisalo-Repo, M., Ranta, P., Maki, T., Kautiainen, H., Hannonen, P., Korpela, M., Hakala, M., Jarvinen, P., Mottonen, T., 2007. Serum IL-1β levels are associated with the presence of erosions in recent onset rheumatoid arthritis. *Clinical and Experimental Rheumatology*, Vol. 25, pp. 684-689.
11. El-Kady, I.M. and El-Masry, S.A., 2008. Pro-inflammatory and anti-inflammatory cytokines profile in rheumatoid arthritis patients. *The Egyptian Journal of Immunology / Egyptian Association of Immunologists*, Vol. 15, Issue 1, pp. 109-114.
12. Feldmann, M., 1996. Role of cytokines in rheumatoid arthritis. *Annual Review of Immunology*, Vol. 14, pp. 397–440.
13. Fiorentino, D.F., Bond, M.W., Mosmann, T.R., 1989. Two types of mouse T helper cell. IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones. *The*

Journal of Experimental Medicine, Vol. 170, Issue 6, pp. 2081-2095.

14. Gabay, C., 2006. Interleukin-6 and chronic inflammation. *Arthritis Research & Therapy,* Vol. 8, Supplement 2, S3.
15. Goronzy, J.J. and Weyand, C.M., 2009. Developments in the scientific understanding of rheumatoid arthritis. *Arthritis Research & Therapy,* Vol. 11, Issue 5, pp. 249.
16. Horai, R., Saijo, S., Tanioka, H., Nakae, S., Sudo, K., Okahara, A., Ikuse, T., Asano, M., Iwakura, Y., 2000. Development of chronic inflammatory arthropathy resembling rheumatoid arthritis in interleukin-1 receptor antagonist-deficient mice. *The Journal of Experimental Medicine,* Vol. 191, Issue 2, pp. 313-320.
17. Hu, X., 2002. Sensitization of IFN-γ Jak-STAT signaling during macrophage activation. *Nature Immunology*, Vol. 3, Issue 9, pp. 859–866.
18. Joosten, L.A., Helsen, M.M., Saxne, T., Van De Loo, F.A., Heinegard, D., Van Den Berg, W.B., 1999. IL-1 alpha beta blockade prevents cartilage and bone destruction in murine type II collagen-induced arthritis, whereas TNF-α blockade only ameliorates joint inflammation. The *Journal of Immunology*, Vol. 163, pp. 5049-5055.
19. Keffer, J., Probert, L., Cazlaris, H., Georgopoulos, S., Kaslaris, E., Kioussis, D., Kollias, G., 1991. Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis. *The EMBO Journal*, Vol. 10, Issue 13, pp. 4025-4031.
20. Kokkonen, H., Soderstrom, I., Rocklov, J., Hallmans, G., Lejon, K., Dahlqvist, S.R., 2010. Up-regulation of cytokines and chemokines predates the onset of rheumatoid arthritis. *Arthritis and Rheumatism,* Vol. 62, Issue 2, pp. 383-391.
21. Kong, Y.Y., 1999. Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand. *Nature*, Vol. 402, pp. 304–309.
22. Marcouiller, P., Pelletier, J.P., Guevremont, M., Martel-Pelletier, J., Ranger, P., Laufer, S., Reboul, P., 2005. Leukotrienes and Prostaglandin synthesis pathways in osteoarthritic synovial membranes: regulating factors for interleukin 1β synthesis. *The Journal of Rheumatology,* Vol. 32, Issue 4, pp. 704-712.
23. Mathis, S., Jala, V.R., Haribabu, B., 2007. Role of leukotrienes-B4 receptors in rheumatoid arthritis. *Autoimmunity Reviews,* Vol. 7, Issue 1, pp. 12-17.
24. Matsuoka, N., 1991. Phenotypic characteristics of T cells interacted with synovial cells. *The Journal of Rheumatology*, Vol. 18, Issue 8, pp. 1137–1142.
25. Nagy, G., Clark, J.M., Buzas, E.I., Gorman, C.L., Cope, A.P., 2007. Nitric oxide, chronic inflammation and autoimmunity. *Immunology Letters*, Vol. 111, Issue 1, pp. 1-5.
26. Peters-Golden, M., 2008. Expanding roles for leukotrienes in airway inflammation. *Current Allergy and Asthma Reports,* Vol. 8, Issue 4, pp. 367-373.
27. Petrovic-Rackov, L. and Pejnovic, N., 2006. Clinical significance of IL-18, IL-15, IL-12 and TNF-α measurement in rheumatoid arthritis. *Clinical Rheumatology,* Vol. 25, Issue 4, pp. 448-452.
28. Proudman, S.M., Cleland, L.G., Mayrhofer, G., 1999. Effects of Tumor necrosis factor-alpha, interleukin 1β, and activated peripheral blood mononuclear cells on the expression of adhesion molecules and recruitment of leukocytes in rheumatoid synovial xenografts in SCID mice. *The Journal of Rheumatology*, Vol. 26, Issue 9, pp. 1877-1889.
29. Qu, Z., Garcia, C.H., O'Rourke, L.M., Planck, S.R., Kohli, M., Rosenbaum, J.T., 1994. Local proliferation of fibroblast-like synoviocytes contributes to synovial hyperplasia. Results of proliferating cell nuclear antigen/cyclin, c-myc, and nucleolar organizer region staining. *Arthritis & Rheumatology*, Vol. 37, Issue 2, pp. 212–220.
30. Svensson, L., Jirholt, J., Holmdah, R., Jansson, L., 1998. B-cell-deficient mice do not develop type II collagen-induced arthritis (CIA). *Clinical and Experimental Immunology,* Vol. 111, Issue 3, pp. 521-526.
31. Taylor, P.C., Feldmann, M., 2004. Rheumatoid arthritis: pathogenic mechanisms and therapeutic targets. *Drug Discovery Today: Disease Mechanism*, Vol. 1, Issue 3, pp. 289 295.
32. Zwerina, J., Redlich, K., Schett, G., Smolen, J.S., 2005. Pathogenesis of rheumatoid arthritis: targeting cytokines. *Annals of New York Academy of Sciences*, Vol. 1051, pp. 716–729.

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