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Interleukin-10 and Receptors in Treatment Rheumatoid Arthritis

Koikoi Kebe Bilivogui[1], Ansoumane Kourouma[2], Cai liping[1], Li xiao Yi[1], Xiongwen Wu[1*]

[1] *Department Immunology, School of Basic Medical Sciences, Huazhong University of Sciences and Technology, Tongji Medical College Add: 13 Hangkong Road, Hankou, and Wuhan, Hubei, China 430030*
[2] *MOE Key Laboratory of Environmental and Health, Department of Occupational and Environmental Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, 13 Hangkong Road, Wuhan 430030, People's Republic of China*

Abbreviation:
RA Rheumatoid arthritis.
IL-10 Interleukin -10.
rIL-10 Recombinant Interleukin -10 receptor.
IL-1 Interleukin 1
CD Cluster of differentiation.
TNF Tumor necrosis factor
TH T-helper.
CFR2 Cytokine family receptor type2.
LPS Lipopolysaccharide.
DCs Dendritic cells.
JAK Janus kinase
STAT Signal transducer and activator of transcription
Bcl B cell leukemia
NF-kB Nuclear factor-kappa B
KDa kilo Dalton
Treg T regulator.

Abstract: *The progressive destruction of cartilage and bone in rheumatoid arthritis(RA) cause substantial effects in the synovial membrane and, this is dangerous for rheumatoid arthritis patients, macrophages play a potent stimulating role in synovial inflammation. Accordingly, we purposed in this review to study both treatment of AR by interleukin 10 (IL-10), and receptors with signalization pathway IL-10/Jak/Stat3. Recent work indicates that the production of IL-10 in a target is important in animal models for the relief of AR. Previous studies on animals have provided that IL-10 administration could ameliorate the symptoms of AR. In addition, IL-10 receptors (rIL-10) application in human clinical test versus in AR date a decade. It is unbelievable that the toleration of IL-10 was very better in contrast with other cytokines, and also the efficacy and tolerability of human IL-10 for CD. However, the identification of IL-10, and the role of IL-10 within synovial joints, established in rheumatoid arthritis is poorly understood incompletely with an insufficient knowledge of its biology.is still limited. Further studies are very important for discovering of a new immunotherapy of rheumatoid arthritis treatment by IL-10. Therefore, we discuss new insights into IL-10 regulation of the inflammatory response in AR.*

Keywords: *rheumatoid arthritis, IL-10, inflammation, immunotherapy, macrophage.*

I. Introduction

In the last decade, autoimmune diseases have become a serious problem for public health worldwide. However, in Rheumatoid arthritis, macrophages play a potent critical stimulating role in synovial inflammation by producing proinflammatory cytokines (IL-1, TNF). The interaction between genetic and environmental factors causes inflammation synovial tissues of rheumatoid arthritis [1], but previous studies have showed that IL-10 seemed to be a promising treatment for rheumatoid arthritis by its capacity to deactivate macrophages, and activate CD4 (T helper) and inhibit immune cells. Few recent studies reported that IL-10, a potent anti-inflammatory cytokine, has been demonstrate to inhibit immune cells in rheumatoid arthritis in animal model [2] and human [3], therefore it is a very important anti-inflammatory factor . However, there is evidence that failure resolved in rheumatoid arthritis is often due to the result of insufficient immune response or an imbalance between proinflammatory [4] and anti-inflammatory cytokine and used drugs, cost, secondary effects. In this present study, we purpose to study IL-10 and receptors (pathway) for the treatment of rheumatoid arthritis,

without any secondary effects which protecting environmental tissues Therefore, in this mini-review, the contribution to research of Rheumatoid arthritis treatment by IL-10 and receptors is very interesting, but this study is not a full review. The aim of this study is of finding the improvement on the quality of immunotherapy treatment in rheumatoid arthritis by IL-10 and receptors with a low cost, without any secondary effects for rheumatoid arthritis patients and also environmental tissues protecting by inhibiting the activities of macrophages and immune cells by reducing their hypersensitivity. We therefore showed IL-10 as a key for cytokine proinflammatory response; because it has the unique capacity to down regulate the production of many proinflammatory cytokines, their receptors act into concert to stop the signalization pathway of the macrophages and immune cells activity in the synovial membrane. Our hypothesis is that rheumatoid arthritis may be treated by IL-10 and receptors. This research allows us to postulate the hypothesis that IL-10 is capable to inhibit the activities of the pro-inflammatory cytokines (TH17, TNF, IL-1 β, IL-6) through anti-inflammatory that plays a potent pathogenesis role in rheumatoid arthritis, which is the aim of our mini-review.

Rheumatoid arthritis: It is apparent that rheumatoid arthritis is a severe autoimmune disease joint inflammation and the formation pannus tissue due to the synovial hyperplasia, which causes inflammatory cells (TNF-α, IL-1β, IL-6) and mononuclear cells recruitment for the destruction of cartilage and bone, macrophages play a potent role in synovial inflammation [5]. In rheumatoid arthritis the synovial fluid autoimmune is characterized by infiltrate cells innate and cells adaptive immune systems that can lead to the development of lymphoid tissue. [6, 7], but the dendritic cells may also play a negative role in antigen presentation causing many autoimmune lesions [8, 9]. This disease affects over 1% of people in U S A and 0.25-0.50% of the French population alone [10].

Interleukin-10 and receptor

Recent, studies reported that IL-10 is a multifunctional cytokine secreted primarily by a variety of cells such as macrophage, regulatory T cells, B cells, and epithelial cells. IL-10 family cytokine have been identified as novel molecules. This family now includes IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28A, IL28B, and 29[11, 12]. However, IL-10 inhibit the production of proinflammatory cytokines (Tumor necrosis factor-α,IL-1b,IL-6,IL-12 and co stimulatory molecules), at the same time inhibiting natural killer cells, suppressing secretion of TH1, deactivating of macrophages [13], and stimulating proliferation of antigen-specific B cell [14]. Furthermore, from deactivated macrophage and dendritic cells, a process that requires the activation of STAT3 [12, 15-17]. IL-10 is also an immunoregulator cytokine key, because its deficiency had been associated with an increased susceptibility in intestinal inflammation [11], infection by HIV-1 and rheumatoid arthritis in mice. Some studies has reported that IL-10 is a potent anti-inflammatory cytokine found in these mice Th2 cells [18],and, it is an immunoregulator cytokine capable for inhibiting inflammation in various pathophysiological tuning. The receptor of IL-10 is very complex IL-10R1 and IL-10R2[19] prove the sequence human IL-10R1 has 578 amino ,with a 90-110 kDa glycosylation protein, but appertain to CRF2(cytokine receptor family type2) [20]. Although IL-10R1 and IL-10R2, work together for the regulation of the body in the IL-10 signaling pathway, but don't have the same objective [21, 22].

In addition, recently, studies showed that IL-10R2 can connected with IL-26,IL-28 and IL-29 signaling pathway and it appertain to CRF2, while IL-10R1 expressed with a low level in overt hematopoietic tissues for production 100-800 molecule per cell [23]. IL-10R2 is non-specific of receptor complexes while IL-10R1 is specific on them. However, the mechanism that induces IL-10 in rheumatoid arthritis synovial is slow unraveled. Lipopolysaccharide (LPS) in vitro is a potent inducer of the secretion of IL-10 by monocytes well, so, the studies prove that IL-1 endogenous tumor necrosis factor (TNF) or downstream of LPS [24]. Other studies have provided that in the rheumatoid arthritis, the synovial has to be established in the macrophages in close contact with T cells inflamed interstitial such as joints [25]. The immunosuppressive and anti-inflammatory cytokine effect of IL-10 plays key role in the treatment potential therapeutic in several autoimmune diseases such as Crohn's, psoriasis disease and rheumatoid arthritis, according to clinical observation [19].

Relevance of this study: Now, we know that rheumatoid arthritis is the human autoimmune disease with prevalence of 0.5- 1% in the world population ;0.8 of people in U S A and 0.25-0.5% in France, West Africa and Asia with 60-65 years and the sex ratio 1, but the real causes is unknown, in spite of progress of the etiology [26]. Nevertheless the pro-inflammatory cytokines have caused a potent damage on the synovial and bone. And in vitro, the induction in rats of 0,1ml of FCA containing 0.05%w/vMB and paraffin oil of the left foot of the rats in 7-28 days after immunization has caused rheumatoid arthritis [27]. Whereas now IL-10 has to be produced by multiple cells such as TH1 [28, 29].TH2 [29, 30]. B cells [31] [32]. Treg [33] Th9 [34] Th17 [35]. Denditric cells (DC) [36, 37]. NK, [38]. Th22 [39]. Macrophages [40], monocytes [41], eosiphilis [42], and others innate immune cells [38]. And, IL-10RA is expressed on NK, various immunology cells. The activity of

Th17 is stopped by CD4+CD25+ of regulator T cells (Treg) [43, 44]. Then, the ratio Th17/Treg is potent on the decrease of rheumatoid arthritis [45, 46], because IL-10 is secreted in large quantity by Treg than Th17.
In addition, several cytokines, anti-inflammatory (anti-TNF) and drugs (NSAIDs, corticosteroids) anti-arthritis have been used in the treatment against RA [47]. But, we observed that, their high cost, secondary effects major are unbearable for rheumatoid arthritis patients. These necessities for researchers to find a new immunotherapy for the treatment of rheumatoid arthritis.

Treatment of IL-10 in rheumatoid arthritis

In animal models: It had been described by analogous studies that IL-10 was a synthesis-inhibitor factor because its capacity to inhibit cytokine production by mouse TH1 cells. [18]. And we observed that IL-10 is a capable to conserve in joint puffiness and transformation in an animal models of rheumatoid arthritis [48], because the autoimmune disease of mice is worsen by deficiency in IL-10. Furthermore, the collagen-induced arthritis (CIA) is similar pathological features of many auto-immune diseases such as rheumatoid arthritis in an animal model, because we finding in the tissues of mice (CIA) that received neutralizing anti-IL-10 antibodies has a capacity to developed quickly a more severe auto-immune disease such as rheumatoid arthritis. Therefore, at the same times, we analyzed that the single daily murine IL-10 i.p injection (5µg/day) can inhibited clinical disease progression active in collagen type II-induced arthritis rheumatoid in mice [49]. In addition, we also followed the treatment by IL-10 in vivo during 48days a pre-clinical at a dose 100ng/day can suppress the clinical severity of collagen-induced arthritis rheumatoid in DBA/1 mice [50]. After the analysis of the previous studies, we find that the studies animal models showed that IL-10 is a potent basis for the clinical development and a possible treatment of rheumatoid arthritis.

In human: we also understood that IL-6, has responsible for synovitis because its causing destruction in cartilage and bone tissue [51], and thus, IL-10 has a potent effect on the synovitis and on B cells activation for antibody production, inhibiting antigen presentation and macrophage activation [52]. Nevertheless, clinical observation of IL-10 in human showed an immunomodulatory role of this cytokine in 17 healthy persons. We analyzed that the alone intravenous infusion 25µg/kg of IL-10 has played a role for product transitory in neutrophilia, monocytosis, and lymphopenia [3]. IL-10 infusion can inhibited the proliferation of peripheral blood MNCs and in set blood cultures, this stimulated the production of TNFα and IL-1 decreased LPS [3]. The platelet counts quickly normalized after stopping the IL10 injection. Then, the single doses of IL-10 which causes no significant toxicity are very important for this study. Thus, so far in the human rheumatoid arthritis, the IL-10 receptor decrease has never been confirmed.
However, others studies are in progress to evaluate the clinical treatment by IL10 for rheumatoid arthritis in human. In conclusion, we observed data about IL-10 and the findings suggest possibilities of new approach to the treatment of rheumatoid arthritis by interleukin 10and receptors.

Signalization pathway IL-10

Inflammation is an overriding factor of threat to rheumatoid arthritis and the complex molecular trigger inflammation of infection in mammals [53, 54,55] but, it is not the leading cause of autoimmune diseases; It is a very important contributing factor [56]. This study has showed a general consensus that, IL-10 is a potent immunosuppressive cytokine because its capacity of inhibition in immune cells but its activity must be strictly regulated. However, the effects of IL-10, considered to be limited in macrophages, dendritic cells and lymphocytes, it exerts effects through two distinct channels (receptors IL-10R1 and IL-10R2). IL-10R1 is restricted to leukocytes; meanwhile IL-10R2 is comparatively expressed [57]. And then IL-10 activates the IL-10R/JAK1/STAT3 in waterfall, where phosphorylated STAT3 homodimers are translocating to the nucleus to activate the expression of genes. As showed Figure 1, IL-10R/JAK/STAT3 which is the signalization pathway led to some clear conclusions beforetime recapitulated by Murray [2], IL-10 can also inhibit cytokine production in neutrophils [58]. IL-10 has a key mechanism for deactivation of activated macrophages and inflammatory mediators by Stat3 [59, 60].

In addition, the anti-inflammatory effect of IL-10 in macrophage or in others cells, manifests as the transcriptional inhibition of Lipopolysaccharide, induction the proinflammatory mediators [61]. The Jak1 and Tyk2 interact with member's family IL-10Ra respectively [62]. In a ligand-independent fashion IL-10 can provoked heterodimerization leads to activate on the Jak1 and phosphorilation of the Il-10Ra in the cytoplasm tyrosine. And these residues form docking sites for members of the STAT family of transcription factors; Stat3 is directing, recruited to IL-10Ra and turn into phosphorylated by receptor-associated Jak kinase. Thus Stat3 can stimulates the expression genes with the expression of proinflammatory gene .The various factors have been identified such Bcl3 works by impairing NFkB's capacity to bind DNA, TFN-production has suppressing [63,

64]; Etv3, a transcriptional co-receptor that inhibits NFkB's activity [65]; SHIP-1 can inhibited the TNF translation which Stat3-indepent mechanism. ABIN-3 which inhibits NFkB activation but is dispensable in human [66].

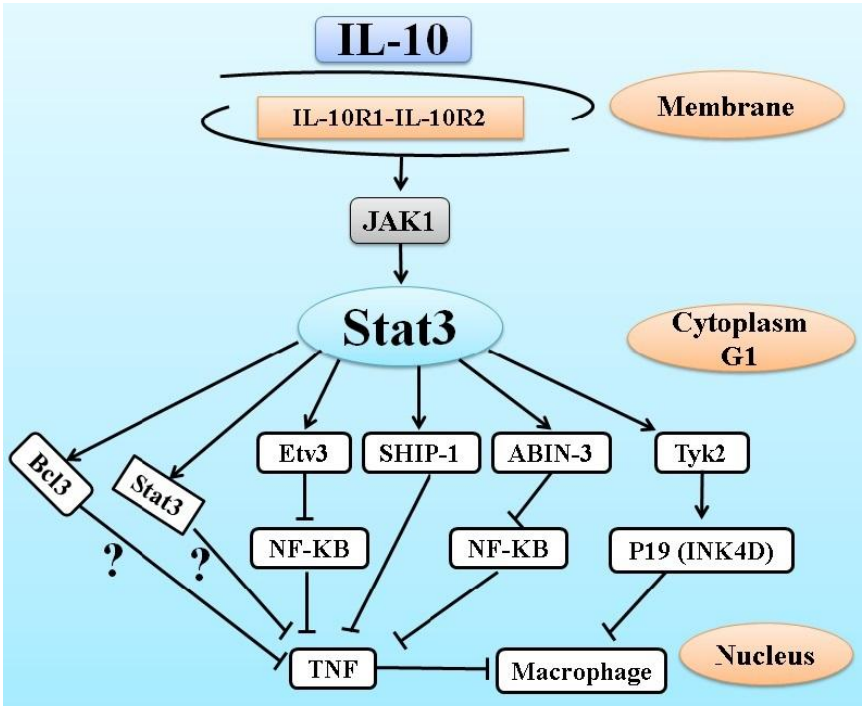

Figure 1: The proposed diagram may to explain the inhibition of all pro-inflammatory and mediators by IL-10 and receptors are induced by LPS (Lipopolysaccharide) stimulation.IL-10 initiates by IL-10R the jak1 phosphorylates or the Stat3 and factors. From the cell membrane to cytoplasm, to on entering the nucleus, Stat3 activates the expression of proinflammatory genes at transcriptional level with the genes activates by LPS in macrophages ultimately being inhibited by IL-10 [2]. And also,IL-10 can induce STAT3 pathway which act concert which p19INk4D to inhibit macrophages , the Stat3-dependen induction of $p^{19INK4D}$ is very interesting of the mechanism by which IL-10 blocks proliferation in macrophages in the nucleus is important for treatment of rheumatoid arthritis by interleukin-10.

In addition, the growth stopping by IL-10 is Stat3-dependent and requires two membrane-distal tyrosine of the IL-10Ra, by $p^{19INK4D}$. This involvement that activation of Stat3 is sufficient for inhibition of macrophages (J774) proliferation, and, amply that p19 is principal for optimal inhibition of proliferation of macrophage by IL-10, it indicating that IL-10 regulates promoter activity through Stat3 in Rheumatoid arthritis. IL-10 can induce additional cell cycle which acts in concert with $_p$19INK4D to inhibit macrophage (J774) and cell cycle progression (G1).

This study concludes that IL-10 and STAT3 are essential for Rheumatoid arthritis and cannot be replaced by any other cytokine for their work in antagonism to inhibit the proinflammatory cytokines [67].

References

[1]. Nordang, G.B., et al., Association analysis of the interleukin 17A gene in Caucasian rheumatoid arthritis patients from Norway and New Zealand. Rheumatology, 2009. **48**(4): p. 367-370.
[2]. Murray, P.J., Understanding and exploiting the endogenous interleukin-10/STAT3-mediated anti-inflammatory response. Current opinion in pharmacology, 2006. **6**(4): p. 379-386.
[3]. Chernoff, A.E., et al., A randomized, controlled trial of IL-10 in humans. Inhibition of inflammatory cytokine production and immune responses. The Journal of Immunology, 1995. **154**(10): p. 5492-5499.
[4]. Romagnani, S., Lymphokine production by human T cells in disease states. Annual review of immunology, 1994. **12**(1): p. 227-257.
[5]. Refaat, R., et al., Evaluation of the effect of losartan and methotrexate combined therapy in adjuvant-induced arthritis in rats. European journal of pharmacology, 2013. **698**(1): p. 421-428.
[6]. Wagner, U.G., et al., The role of CD8+ CD40L+ T cells in the formation of germinal centers in rheumatoid synovitis. The Journal of Immunology, 1998. **161**(11): p. 6390-6397.
[7]. Pettit, A.R., et al., Differentiated dendritic cells expressing nuclear RelB are predominantly located in rheumatoid synovial tissue perivascular mononuclear cell aggregates. Arthritis & Rheumatism, 2000. **43**(4): p. 791-800.

[8]. Ludewig, B., et al., Dendritic cells induce autoimmune diabetes and maintain disease via de novo formation of local lymphoid tissue. The Journal of experimental medicine, 1998. **188**(8): p. 1493-1501.
[9]. Ma-Krupa, W., et al., Activation of arterial wall dendritic cells and breakdown of self-tolerance in giant cell arteritis. The Journal of experimental medicine, 2004. **199**(2): p. 173-183.
[10]. Imboden, J.B., The immunopathogenesis of rheumatoid arthritis. Annual Review of Pathological Mechanical Disease, 2009. **4**: p. 417-434.
[11]. Glocker, E.O., et al., IL-10 and IL-10 receptor defects in humans. Annals of the New York Academy of Sciences, 2011. **1246**(1): p. 102-107.
[12]. Ouyang, W., et al., Regulation and functions of the IL-10 family of cytokines in inflammation and disease. Annual review of immunology, 2011. **29**: p. 71-109.
[13]. Bogdan, C., Y. Vodovotz, and C. Nathan, Macrophage deactivation by interleukin 10. The Journal of experimental medicine, 1991. **174**(6): p. 1549-1555.
[14]. Williams, L.M., et al., Interleukin-10 suppression of myeloid cell activation—a continuing puzzle. Immunology, 2004. **113**(3): p. 281-292.
[15]. Hofmann, S., et al., Biological properties and regulation of IL-10 related cytokines and their contribution to autoimmune disease and tissue injury. Clinical immunology, 2012. **143**(2): p. 116-127.
[16]. Kubo, M. and Y. Motomura, Transcriptional regulation of the anti-inflammatory cytokine IL-10 in acquired immune cells. Frontiers in immunology, 2012. **3**.
[17]. Paul, G., V. Khare, and C. Gasche, Inflamed gut mucosa: downstream of interleukin-10. European journal of clinical investigation, 2012. **42**(1): p. 95-109.
[18]. Fiorentino, D.F., M.W. Bond, and T. Mosmann, 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, 1989. **170**(6): p. 2081-2095.
[19]. Crepaldi, L., et al., Up-regulation of IL-10R1 expression is required to render human neutrophils fully responsive to IL-10. The Journal of Immunology, 2001. **167**(4): p. 2312-2322.
[20]. Kotenko, S.V. and S. Pestka, Jak-Stat signal transduction pathway through the eyes of cytokine class II receptor complexes. Oncogene, 2000. **19**(21): p. 2557-2565.
[21]. Sheppard, P., et al., IL-28, IL-29 and their class II cytokine receptor IL-28R. Nat Immunol, 2003. **4**(1): p. 63-8.
[22]. Sheikh, F., et al., Cutting edge: IL-26 signals through a novel receptor complex composed of IL-20 receptor 1 and IL-10 receptor 2. The Journal of Immunology, 2004. **172**(4): p. 2006-2010.
[23]. Jurlander, J., et al., Characterization of interleukin-10 receptor expression on B-cell chronic lymphocytic leukemia cells. Blood, 1997. **89**(11): p. 4146-4152.
[24]. Foey, A.D., et al., Regulation of monocyte IL-10 synthesis by endogenous IL-1 and TNF-α: role of the p38 and p42/44 mitogen-activated protein kinases. The Journal of Immunology, 1998. **160**(2): p. 920-928.
[25]. Duke, O., et al., An immunohistological analysis of lymphocyte subpopulations and their microenvironment in the synovial membranes of patients with rheumatoid arthritis using monoclonal antibodies. Clinical and experimental immunology, 1982. **49**(1): p. 22.
[26]. Ziff, M., The rheumatoid nodule. Arthritis & Rheumatism, 1990. **33**(6): p. 761-767.
[27]. Singh, S., V. Nair, and Y. Gupta, Antiarthritic activity of Majoon Suranjan (a polyherbal Unani formulation) in rat. The Indian journal of medical research, 2011. **134**(3): p. 384.
[28]. Anderson, C.F., et al., CD4+ CD25− Foxp3− Th1 cells are the source of IL-10–mediated immune suppression in chronic cutaneous leishmaniasis. The Journal of experimental medicine, 2007. **204**(2): p. 285-297.
[29]. Saraiva, M., et al., Interleukin-10 production by Th1 cells requires interleukin-12-induced STAT4 transcription factor and ERK MAP kinase activation by high antigen dose. Immunity, 2009. **31**(2): p. 209-219.
[30]. Veldhoen, M., et al., Transforming growth factor-β'reprograms' the differentiation of T helper 2 cells and promotes an interleukin 9–producing subset. Nature immunology, 2008. **9**(12): p. 1341-1346.
[31]. Fillatreau, S., D. Gray, and S.M. Anderton, Not always the bad guys: B cells as regulators of autoimmune pathology. Nature Reviews Immunology, 2008. **8**(5): p. 391-397.
[32]. Maynard, C.L. and C.T. Weaver, Diversity in the contribution of interleukin-10 to T-cell-mediated immune regulation. Immunological reviews, 2008. **226**(1): p. 219-233.
[33]. Boden, E.K. and S.B. Snapper, Regulatory T cells in inflammatory bowel disease. Current opinion in gastroenterology, 2008. **24**(6): p. 733-741.
[34]. Li, H., et al., Cyclooxygenase-2 inhibits T helper cell type 9 differentiation during allergic lung inflammation via down-regulation of IL-17RB. American journal of respiratory and critical care medicine, 2013. **187**(8): p. 812-822.
[35]. Shoemaker, J., M. Saraiva, and A. O'Garra, GATA-3 directly remodels the IL-10 locus independently of IL-4 in CD4+ T cells. The Journal of Immunology, 2006. **176**(6): p. 3470-3479.
[36]. Boonstra, A., et al., Macrophages and myeloid dendritic cells, but not plasmacytoid dendritic cells, produce IL-10 in response to MyD88-and TRIF-dependent TLR signals, and TLR-independent signals. The Journal of Immunology, 2006. **177**(11): p. 7551-7558.
[37]. Dillon, S., et al., Yeast zymosan, a stimulus for TLR2 and dectin-1, induces regulatory antigen-presenting cells and immunological tolerance. Journal of Clinical Investigation, 2006. **116**(4): p. 916.
[38]. Ryan, J.J., et al., Mast cell homeostasis: a fundamental aspect of allergic disease. Critical Reviews™ in Immunology, 2007. **27**(1).
[39]. Wolk, K., et al. Biology of interleukin-22. in Seminars in immunopathology. 2010. Springer.
[40]. Jenkins, J., M. Malyak, and W. Arend, The effects of interleukin-10 on interleukin-1 receptor antagonist and interleukin-1 beta production in human monocytes and neutrophils. Lymphokine and cytokine research, 1994. **13**(1): p. 47-54.
[41]. de Waal Malefyt, R., et al., Interleukin 10 (IL-10) inhibits cytokine synthesis by human monocytes: an autoregulatory role of IL-10 produced by monocytes. The Journal of experimental medicine, 1991. **174**(5): p. 1209-1220.
[42]. Alanara, T., et al., Expression of IL-10 family cytokines in rheumatoid arthritis: elevated levels of IL-19 in the joints. Scand J Rheumatol, 2010. **39**(2): p. 118-26.
[43]. Chaudhry, A., et al., CD4+ regulatory T cells control TH17 responses in a Stat3-dependent manner. Science, 2009. **326**(5955): p. 986-991.
[44]. Ogino, H., et al., CD4+ CD25+ regulatory T cells suppress Th17-responses in an experimental colitis model. Digestive diseases and sciences, 2011. **56**(2): p. 376-386.
[45]. Duarte, J., et al., Modulation of IL-17 and Foxp3 expression in the prevention of autoimmune arthritis in mice. PloS one, 2010. **5**(5): p. e10558.

[46]. Nistala, K. and L.R. Wedderburn, Th17 and regulatory T cells: rebalancing pro-and anti-inflammatory forces in autoimmune arthritis. Rheumatology, 2009. **48**(6): p. 602-606.
[47]. Gibofsky, A., Comparative effectiveness of current treatments for rheumatoid arthritis. The American journal of managed care, 2012. **18**(13 Suppl): p. S303-14.
[48]. Ying, B., et al., Association of polymorphisms in the human IL-10 and IL-18 genes with rheumatoid arthritis. Molecular biology reports, 2011. **38**(1): p. 379-385.
[49]. Walmsley, M., et al., Interleukin-10 inhibition of the progression of established collagen-induced arthritis. Arthritis & Rheumatism, 1996. **39**(3): p. 495-503.
[50]. Tanaka, Y., et al., Effect of IL-10 on collagen-induced arthritis in mice. Inflammation Research, 1996. **45**(6): p. 283-288.
[51]. Henningsson, L., et al., Disease-dependent local IL-10 production ameliorates collagen induced arthritis in mice. PloS one, 2012. **7**(11): p. e49731.
[52]. Moore, K.W., et al., Interleukin-10 and the interleukin-10 receptor. Annual review of immunology, 2001. **19**(1): p. 683-765.
[53]. Medzhitov, R., Origin and physiological roles of inflammation. Nature, 2008. **454**(7203): p. 428-435.
[54]. Simonatto, M. and G. Natoli, Functional genomics of the inflammatory response: where are we now? Brief Funct Genomics, 2013. **12**(6): p. 483-8.
[55]. Takeuchi, O. and S. Akira, Pattern recognition receptors and inflammation. Cell, 2010. **140**(6): p. 805-820.
[56]. Nathan, C. and A. Ding, Nonresolving inflammation. Cell, 2010. **140**(6): p. 871-882.
[57]. Yoon, S.I., et al., Conformational changes mediate interleukin-10 receptor 2 (IL-10R2) binding to IL-10 and assembly of the signaling complex. Journal of Biological Chemistry, 2006. **281**(46): p. 35088-35096.
[58]. Cassatella, M.A., et al., Lipopolysaccharide primes neutrophils for a rapid response to IL-10. European journal of immunology, 2005. **35**(6): p. 1877-1885.
[59]. Koppelman, B., et al., Interleukin-10 down-regulates MHC class II alphabeta peptide complexes at the plasma membrane of monocytes by affecting arrival and recycling. Immunity, 1997. **7**(6): p. 861-71.
[60]. Song, S., et al., Interleukin-10 inhibits interferon-gamma-induced intercellular adhesion molecule-1 gene transcription in human monocytes. Blood, 1997. **89**(12): p. 4461-9.
[61]. Lang, R., et al., Shaping gene expression in activated and resting primary macrophages by IL-10. The Journal of Immunology, 2002. **169**(5): p. 2253-2263.
[62]. Kotenko, S.V., et al., Identification and functional characterization of a second chain of the interleukin-10 receptor complex. The EMBO journal, 1997. **16**(19): p. 5894-5903.
[63]. Kuwata, H., et al., IL-10-inducible Bcl-3 negatively regulates LPS-induced TNF-α production in macrophages. Blood, 2003. **102**(12): p. 4123-4129.
[64]. Hutchins, A.P., et al., Distinct transcriptional regulatory modules underlie STAT3's cell type-independent and cell type-specific functions. Nucleic acids research, 2013. **41**(4): p. 2155-2170.
[65]. El Kasmi, K.C., et al., Cutting edge: A transcriptional repressor and corepressor induced by the STAT3-regulated anti-inflammatory signaling pathway. The Journal of Immunology, 2007. **179**(11): p. 7215-7219.
[66]. Weaver, B.K., et al., ABIN-3: a molecular basis for species divergence in interleukin-10-induced anti-inflammatory actions. Molecular and cellular biology, 2007. **27**(13): p. 4603-4616.
[67]. Braun, D.A., M. Fribourg, and S.C. Sealfon, Cytokine response is determined by duration of receptor and signal transducers and activators of transcription 3 (STAT3) activation. Journal of Biological Chemistry, 2013. **288**(5): p. 2986-2993.