Chin J Integr Med 2013 Nov;19(11):874-880

REVIEW

How Does Chinese Medicine Target Cytokine Imbalance in Rheumatoid Arthritis?*

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ABSTRACT Rheumatoid arthritis (RA) manifests as an imbalance between pro- and anti-inflammatory cytokines. Cytokine imbalance is suggested to play critical roles in the development of RA. Currently, various treatments for RA, including biological agents such as antibodies against inflammation mediators, or Chinese herbal medicines, intervene the disease by restoring the balance of cytokines. Chinese medicine (CM) can not only suppress the expression of pro-inflammatory cytokines, but also induce the expression of cytokines with anti-inflammatory and immunomodulatory effects. Thus, Chinese medicine can effectively reduce inflammatory cell infiltration into synovial tissue, pannus formation, and degradation of the extracellular matrix surrounding cartilage cells, thereby reducing subchondral bone damage. This paper reviews the changes of cytokine profiling during development of RA and discuss the mechanisms by which Chinese medicine restores the cytokine balance.

KEYWORDS rheumatoid arthritis, cytokine imbalance, Chinese medicine

Rheumatoid arthritis (RA) is a common autoimmune disease characterized by nonsuppurative proliferative synovitis, which gradually leads to the destruction of articular cartilage lesions resulting in joint dysfunction and systemic disease. Cytokines are protamine molecules, which are expressed in immune cells and non-immune cells and secreted into the extracellular matrix. They help control the immune system and fight diseases. However, abnormalities in cytokine expression can lead to pathological responses. Under normal circumstances, the inflammatory cytokine network requires a lot of anti-inflammatory cytokines to counteract the pro-inflammatory cytokines, in order to maintain the stability of internal environment. The reduction of these anti-inflammatory cytokines can lead to persistent synovial inflammation.[1] The relative effect of the cytokine network relies on the cellular environment and its inhibitor. RA has cytokine balance disorders in which levels of pro-inflammatory cytokines increase and levels of anti-inflammatory factors decrease. This leads to immune-related chronic inflammation. Currently, most treatments for RA, including biological agents and Chinese herbal medicines, intervene the diseases by restoring the cytokine balance. However, the role of cytokine imbalance in the development of RA needs to be further studied.

RA and Cytokine Imbalance

The RA disease state has increased levels of pro-inflammatory cytokines. During the development of RA, some cytokines can initiate inflammatory reactions, which can destruct the articular cartilage. These cytokines include interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, and tissue growth factor (TGF)-β. In certain pathological conditions, these cytokines can produce synergistic biological effects and stimulate the synthesis of synovial cells and chondrocytes. This subsequently causes the absorption of bone and cartilage destruction, and promotes the proliferation of fibroblasts. Cytokines can also promote an increase in the level of rheumatoid factor (RF) and synthesis of other immune globulin, promoting the continued progress of synovitis and resulting in RA cartilage injury.[2,3]

During RA, there is a decrease in the level of anti-inflammatory cytokines (Table 1).[4] In the inflammatory process of RA, some cytokines, which

*Supported by the Key Projects in the National Science and Technology Pillar Program during the Twelfth Five-Year Plan Period (No. 2012BAI26B02); the National Key Disciplines of Chinese Medicine Construction Projects (No. [2009]30); Anhui Technology Scientific Research and Development Program of Provincial Department (No. 11010402170); Technology Innovation Team Program of Anhui University of Chinese Medicine (No. 2010TD005)

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DOI: 10.1007/s11655-013-1620-6

Table 1. Pro-inflammatory and Anti-inflammatory Cytokines in the RA Immune Pathology Process

Category	Pro-inflammatory cytokines	Anti-inflammatory cytokines
Interleukin	IL-1, IL-2, IL-6, IL-7, IL-11, IL-12, IL-15, IL-17, IL-18, IL-21	IL-4, IL-10, IL-35
Tumor necrosis factor	TNF-α, BLyS	
Growth factor	TGF-β, PDGF, VEGF	TGF-β
Chemotactic factor	CXCR3, CXCL16, CCL5, CCL15 RANTES, MIP-1β, MIP-1α, MCP	CCR1, CXCR5
	IFN-γ	

Notes: BLyS: B lymphocyte stimulator; PDGF: platelet-derived growth factor; VEGF: vascular endothelial growth factor; CXCCR3: CXC-chemokine R3; CXCL16: CXC-chemokine ligand 16; CCL5: CC-chemokine ligand 15; RANTES: regulated upon activation normal T-cell expressed and secreted; MIP1β: macrophage inflammatory protein-1β; MCP: monocyte chemoattractant protein-1

can inhibit the inflammatory effects, are generally reduced.[5] These cytokines can inhibit the expression of CD69 and interferon (IFN)-γ by nature killer cells, and reduce the cytotoxity and cytokine secretion of macrophage.[6] The reduced expression of anti-inflammatory cytokines in the RA synovium prompts a lack of protection mechanism. The decrease of cytokines can result in autoimmune disorders in RA patients, which are the main factors causing the clinical symptoms of RA.

Regulation of Drugs for the Treatment of RA on the Cytokine Network

Disease-modifying Anti-rheumatic Drugs Can Modulate Cytokine Balance

There are a variety of arthritis medications called disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate (MTX), leflunomide (LEF), and hydroxychloroquine (HCQ). They work by curbing the underlying processes that cause certain forms of inflammatory arthritis. These drugs not only treat arthritis symptoms, but can also slow down progressive joint destruction. DMARDs can slightly inhibit the activity of pro-inflammatory cytokines like IL-1β, IL-6, TNF-α, and IFN-γ, thus reducing inflammation in RA patients.[7-9] Although considerable progress has been made by adequate treatment with DMARDs, the cure of RA still remains difficult.

Biological Agents Target Cytokines for RA Treatment

The discovery of the importance of cytokines such as TNF-α, IL-1, IL-6, and IL-15, which are stimulated by autoimmune responses, has led to the development of anticytokine therapies ("biologicals"). Biological agents have a more explicit target for RA.

TNF-α blockers, IL-1 receptor antagonists (tIL-1Ra), and the monoclonal antibody of IL-6Rα, can effectively improve RA when DMARD treatment is ineffective. Most of RA patients with biological therapy have significantly improved symptoms. Biological treatment can reduce specific autoantibodies, such as RF, anti-cyclic citrullinated peptide (CCP), anti-nuclear antibody, anti-double-stranded DNA, and antiphospholipid antibody. They can also down-regulate pro-inflammatory cytokines and inflammatory mediators, particularly in synovial tissues.[10,11] Conversely, some potential therapeutic targets can increase the activity of anti-inflammatory factors, which has counter-regulatory effect in contrast to the targeted cell factors, such as IL-4 and IL-10. There are some concerns about the use of IL-21 receptor fusion protein (IL-21R.Fc) in the treatment of type Ⅱ collagen-induced arthritis (CIA) model rats and Freund's complete adjuvant arthritis-model rats.[12]

Although clinical remission is difficult to achieve even with anticytokine treatment, these drugs offer the potential to decrease disease activity and improve the quality of life in a majority of RA patients, and it is conceivable that combinations of biological therapies may pave the way to success, which is ultimately remission.

Chinese Medicine Could Adjust the Cytokine Network of RA

Chinese medicine can play an important role in the treatment of RA, mainly by regulating cytokine network balance. Single Chinese herbs, such as *Salvia miltiorrhiza*, *Cornus officinalis*, *Gardenia*, and *Astragalus*, Chinese medicine monomers, such as Tripterygium glycosides, sinomenine, and ligustrazine, and Chinese medicine compounds, such as Duhuo Jisheng Decoction (独活寄生汤), Wutou Decoction (乌头汤), and Xinfeng Capsule (新风胶囊), all have different degrees of regulatory effects on cytokines.

Single Chinese Herbs

Salvia miltiorrhiza can lower matrix

metalloproteinases (MMP)-9 levels in CIA rats, and significantly improve the inflammation and prethrombotic states of RA when combined with MTX. This provides evidence for the theoretical basis of the use of Chinese medicine to activate blood circulation and eliminate stasis in RA.[13] *Salvia miltiorrhiza* can also somewhat dose-dependently inhibit the secretion of TNF-α.[14] *Cornus officinalis* can reduce CD4+, CD4+/CD8+, and IL-2 levels and the T lymphocyte transformation rate in adjuvant arthritis (AA) rats.[15] Moreover, *Cornus officinalis* glycosides directly inhibit the excessive secretion of inflammatory cytokines produced by monocytes or macrophages, and can reduce inflammatory cell infiltration in synovial tissue, pannus formation, and the degradation of the extracellular matrix surrounding cartilage cells. This can then reduce subchondral bone damage.[16] *Gardenia* can dose-dependently reduce rat paw swelling, and down-regulate the levels of inflammatory factors in AA rats, such as IL-1β and TNF-α.[17] *Astragalus* can markedly promote peripheral blood mononuclear cells to secrete IL-2 in healthy patients, and showed a dose-dependent biphasic effect. Moreover, *Astragalus* can increase the levels of TNF and IFN-γ, *in vitro*, thus enhancing the body's anti-inflammatory function.[18]

Chinese Medicine Effective Components

Tripterygium glycosides can significantly inhibit IL-1, IFN-γ, and MMPs/tissue inhibitors of metalloproteinases (TIMPs), regulate the balance between MMPs/TIMPs, reduce MMP-2, MMP-9, raise TIMP-1, and slow down the corrosion of cartilage and bone, especially in the active stages of RA.[19] Total glucosides of peony can bidirectionally regulate macrophages: they promote the generation of IL-1 at low doses, they inhibit the generation at high doses.[20] When the concentration of prostaglandin E_2 (PGE_2) is low, macrophages generate IL-1, and when PGE_2 concentration is high, macrophages inhibit the secretion of IL-1. Total glucosides of paeony increase IL-2 secretion at low concentrations and lower it at high concentrations. Moreover, total glucosides of paeony can also regulate the generation of IFN-γ. Zhengqing Fengtongning (正清风痛宁, sinomenine) can significantly reduce serum IL-1β and TNF-α in patients with RA, but has no obvious effects on IL-10 content or anti-CCP antibody titer. Expression of TNF-α mRNA, IL-1mRNA, and NF-κB in synovial cells could be dose-dependently inhibited by sinomenine *in vitro*.[21] In addition, sinomenine can effectively inhibit the expression of chemokine receptor CCR5 and CCR7 and its mRNA level in the blood of patients with RA. Sinomenine can also inhibit the secretion of chemotactic factor CXCL9 and CXCL10, but does not affect the expression of CXCL11.[22]

Tetramethylpyrazine can inhibit the expression of hypoxia-inducible factor-1α (HIF-1α), which is the regulatory transcription factor of the vascular endothelial growth factor (VEGF) gene.[23] Glucosides of *Chaenomeles speciosa* can inhibit bone destruction by decreasing IL-2 levels, and inhibit synovial cell function and peritoneal macrophage secretion of TNF-α and IL-1.[24] Triptolide can reduce AA rat serum IL-6 and TNF-α levels in the joint cavity, improve the level of IL-10, inhibit synovial hyperplasia and pannus formation, and reduce the destruction of cartilage and bone.[25] The total saponins of *Radix Clematidis* can reduce cytokine IL-1β, IL-2, IL-6, IL-8, TNF-α, and PGE_2 levels.[26] *Lycopodium clavatum* ethanol extract can significantly decrease serum IL-1β, TNF-α, and IL-6 levels in rats.[27] Artesunate can significantly inhibit the proliferation of synovial cell in CIA rats, and down-regulate synovial cell secretion of TNF-α and IL-1β.[28]

Kirenol can reduce AA rat serum IL-1β, TNF-α, and IL-6 levels, down-regulate the expression of Bcl-2 protein in synovial cells, and promote the expression of Fas-L protein.[29] Emodin can significantly inhibit the release of inflammatory cytokines, significantly reduce IL-1, IL-5, IL-8, and TNF-α, and inhibit the secretion of nitric oxide (NO) dose-dependently.[30] Zaocys hydrolyzate can reduce CIA rat peripheral serum TNF-α level and increase IL-10 level.[31]

Dengzhanxixin Injection (灯盏细辛注射液, *Herba Erigeronis breviscapi*) can improve RA blood stasis symptoms through down-regulation of inflammatory cytokines such as IL-1β and TNF-α. This drug can improve systemic and joint local micro-circulation to promote LEF bioavailability, reducing the side effects of LEF (primarily gastrointestinal reactions) and increasing the tolerance of patients.[32]

Chinese Medicine Compounds

Duhuo Jisheng Decoction (独活寄生汤, *Radix Angelicae pubescentis*, *Ramulus Loranthi*, *Cortex Eucommiae*, *Radix Cyathulae*, *Herba Beesiae calthaefoliae*, *Radix Gentianae Macrophyllae*, *Poria*, *Cinnamomum cassia Presl*, *Radix Saposhnikoviae*,

Rhizoma Ligusticum Wallichii, *Radix Ginseng*, *Radix Glycyrrhizae*, *Radix Angelicae sinensis*, *Radix Paeoniae Alba*, and *Radix Rehmanniae*) can significantly reduce arthritis index and anti-CCP antibody levels, inhibit model rat endogenous IL-1β, and increase IFN-γ levels.[33] Danggui Niantong Decoction (当归拈痛汤, *Herba Artemisiae scopariae*, *Rhizoma et Radix Notopterygii*, *Radix Saposhnikoviae*, *Rhizoma Cimicifugae*, *Radix Puerariae*, *Rhizoma Atractylodis Macrocephalae*, *Radix Glycyrrhizae*, *Radix Scutellariae*, *Radix Sophorae Flavescentis*, *Rhizoma Anemarrhenae*, *Radix Angelicae sinensis*, *Polyporus*, and *Rhizoma Alismatis*) can inhibit TNF-α and IL-1 secretion, increase innate immune function of rat red blood cells, and exert anti-inflammatory and immunomodulatory effects. In synovial lesions, the expression of intercellular adhesion molecular (ICAM)-1 can be inhibited which are highly expressed in AA rat synovial cells. This decoction can also down-regulate VEGF and MMP-3 expression in synovial tissue, reduce angiogenesis, inhibit the formation of pannus, prevent cartilage and subchondral bone erosion, and improve synovial cell apoptotic disorder in AA rats.[34]

Different doses of Wutou Decoction (乌头汤, *Radix Aconiti*, *Astragalus membranaceus* Bge., *Herba Ephedrae, Radix Paeoniae Alba*, and *Radix Glycyrrhizae*) have certain inhibitory effects on AA rat serum IL-1β and TNF-α levels, which inhibits the occurrence of secondary injury, and can reduce joint pain and swelling.[35]

Shentong Zhuyu Decoction (身痛逐瘀汤, *Radix Gentianae Macrophyllae*, *Rhizoma Ligusticum Wallichii*, *Semen Persicae*, *Flos Carthami*, *Radix Glycyrrhizae*, *Rhizoma et Radix Notopterygii*, *Resin Commiphora*, *Radix Angelicae sinensis*, *Faeces Trogopterori*, *Rhizoma Cyperi*, *Radix Cyathulae, Pheretima*, *Rhizoma Atractylodis*, and *Astragalus membranaceus* Bge.) can inhibit AA rat excessive secretion of inflammatory cytokines TNF-α, IL-1, and prostaglandin E_2 (PGE_2), promote and restore a normal microcirculatory state, relieve joint inflammatory cell infiltration and inflammatory synovial proliferation, inhibit the formation of pannus, change synovial cell membrane defects, and decrease the number of inflammatory cells.[36]

Gancao Fuzi Decoction (甘草附子汤, *Radix Glycyrrhizae*, *Radix Aconiti lateralis*, *Rhizoma Atractylodis Macrocephalae, Ramulus Cinnamomi*) can significantly reduce IL-2, TNF-α, and fibroblast growth factor, and up-regulate TGF factor expression in the rat synovium. It can also effectively inhibit the expression of CD4+T cells in synovial tissues of rats, up-regulate the expression of CD8+T cells, and decrease the ratio of T cell subsets.[37] Xinsimiao Decoction (新四妙方, *Rhizoma Smilacis Glabrae*, *Cortex Phellodendri*, *Radix Cyathulae*, and *Radix Cynanchi Paniculati*) inhibits the pro-inflammatory cytokines IL-1, IL-8, and TNF-α, and NO and inducible nitric oxide synthase levels, possibly leading to improvement of anti-inflammatory cytokine IL-10 levels.[38]

Baihu Zhuifeng Pill (白虎追风丸, *Gypsum Fibrosum*, *Ramulus Cinnamomi*, *Semen Coicis*, *Radix Aconiti*, *Radix Paeoniae Alba*, *Herba Asari cum Radice`Radix Angelicae*, and *Radix Glycyrrhizae*) can inhibit AA rat synovial excessive secretion of IL-1 and TNF-α, and excessive release of inflammatory mediators NO and PGE_2. It also inhibits AA rat inflammatory toe swelling, especially secondary swelling.[39] Xuanfa Moyuan Prescription (宣发膜原方, *Radix Dichroae*, *Semen Areca*, *Herba Artemisiae annuae*, *Fructus Tsaoko*, *Rhizoma Anemarrhenae*, *Radix Saposhnikoviae*, etc.) can reduce IFN-γ and TNF-α levels in the serum of CIA rats, increase IL-10, and treat RA by regulating rat serum cytokine content.[40]

Xinfeng Capsule (*Astragalus membranaceus* Bge., *Semen Coicis*, *Caulis Tripterygii Wilfordii*, and *Scolopendra*) can down-regulate IL-1 and TNF-α and up-regulate IL-4 and IL-10 to maintain the balance of Th1/Th2. It can also decrease VEGF levels and platelet parameters, comprehensively regulate T cell immune response, inhibit inflammatory response, enhance anti-inflammatory effects, reduce the production of immune-complex globulin and RF, relieve RA joint symptoms, and improve heart and lung function in patients with RA.[41,42] Biqi Capsule (痹祺胶囊, *Radix Codonopsis*, *Rhizoma Atractylodes Alba*, *Radix Salviae Miltiorrhizae*, *Rhizoma Ligusticum Wallichii*, *Radix Notoginseng*, *Semen Strychni*, etc.) can significantly decrease the abnormal increase of serum IL-1 and TNF-α levels in patients with RA, markedly improve the main symptoms of RA patients. It can also reduce erythrocyte sedimentation rate, RF, and inhibit RA joint injury.[43]

Tongbiling (通痹灵, *Ramulus Cinnamomi*,

Rhizoma Atractylodis Macrocephalae, *Agkistrodon*, *Squama Manitis*, *Radix Dipsaci*, *Radix Paeoniae Alba*, *Rhizoma Anemarrhenae*, *Rhizoma Zingiberis recens*, *Rhizoma Polygonati*, *Radix Saposhnikoviae*, *Semen Strychni*, *Radix Aconiti lateralis*, *Radix Glycyrrhizae*, *Herba Ephedrae*, *Resina Olibanum*, *Scorpio*, *Resin Commiphora*) can reduce IL-1, TNF-α and PGE_2 of synovial cell cultural supernatants in AA rats and down-regulate the expression of IL-1β and TNF-α mRNA in synovial membranes. These effects inhibit joint bone destruction and significantly inhibit the proliferation of synovial fibroblasts.[44]

Xuanbi Granule (宣痹颗粒, *Radix Stephaniae Tetrandrae*, *Fructus Forsythiae*, *Talcum*, *Semen Coicis*, *Fructus Gardeniae, Bombyx mori* L., *Rhizoma Curcumae Longae*, *Cortex Erythrinae orientalis*, *Radix Gentianae Macrophyllae*, *Rhizoma et Radix Notopterygii*) can inhibit inflammatory cytokines such as IL-1β, TNF-α, and IFN-γ and elevate IL-4, balancing Th1/Th2. This drug has good effects on RA during early period of synovitis inflammation, can prevent the formation of pannus, articular cartilage and bone destruction, and suppress joint deformation.[45]

Kunming Shanhaitang Capsule (昆明山海棠胶囊, *Tripterygium hypoglaucum* Hutch.) can significantly decrease CD4+ cell counts in peripheral blood and concurrently decrease the CD4+/CD8+ ratio. It can also improve lymphocyte infiltration in synovial tissue.[46] Bisuqing Mixture (痹速清合剂, *Flos Lonicerae*, *Rhizoma Smilacis Glabrae*, *Cortex Phellodendri*, *Rhizoma Menispermi*, *Caulis Sargentodoxae*, *Semen Coicis*, *Radix Paeoniae rubra*, *Cortex Moutan*, *Radix Paeoniae Alba*, *Herba Asari cum Radice*, *Pericarpium Citri Reticulatae*) can significantly inhibit AA rat primary and secondary joint swelling, appreciably reduce serum levels of TNF-α and IL-1β, elevate IL-4 and IL-10 levels, and increase the body weight of AA rats.[47]

Lijie Capsule (历节胶囊, *Caulis Lonicerae*, *Astragalus membranaceus* Bge., *Semen Coicis*, *Rhizoma Arisaematis*, *Rhizoma Atractylodis*, *Rhizoma Ligusticum Wallichii*, *Radix Paeoniae rubra*, *Radix Angelicae*, *Radix Saposhnikoviae*, etc.) can significantly reduce serum IL-6 in AA rats, improve IL-2 levels, and significantly increase T lymphocyte apoptosis in peripheral blood by mediating the Fas/FasL system.[48] Bitongkang (痹痛康, *Caulis Sinomenii*, *Astragalus membranaceus* Bge., etc.) can inhibit mouse peritoneal macrophage secretion of IL-1 and TNF-α and other inflammatory cytokines. Large, medium and small doses have significant inhibitory effect on the proliferation of T lymphocytes, with an intensity similar to prednisone.[49]

Fengshian Granule (风湿安冲剂, *Rhizoma Anemarrhenae*, *Cortex Phellodendri*, *Astragalus membranaceus* Bge., *Fructus Chaenomelis*, *Caulis Lonicerae*, etc.) can reduce the incidence of arthritis in rats, reduce joint swelling, thymus and spleen mass, and can reduce IL-6 levels of model rats.[50] Qingluo Tongbi Granule (清络通痹颗粒, *Radix Rehmanniae*, *Ramulus Loranthi*, *Caulis Sinomenii*, *Nidus Polistis mandarini*, *Ramulus Euonymi alati*, *Radix Notoginseng*, etc.) can significantly reduce AA rat IL-1 levels produced by peritoneal macrophages, decrease plasma TNF-α, inhibit synovial cells secretion of TNF-α, and reduce pathological damage of joint tissue and cell ultrastructure in AA rats.[51]

Conclusion

RA is a complex pathological process in which cytokine balance is disordered, pro-inflammatory cytokines are increased, and anti-inflammation factors are decreased. The consequence is recurrent inflammation, gradual synovial and cartilage destruction, and disease protraction.

The imbalanced state of pro-inflammatory cytokines and anti-inflammatory cytokines should be corrected in the treatment of RA. Through the reduction of pro-inflammatory cytokines and/or increase of anti-inflammatory cytokines, synovitis could be relieved or prevented. In the future, we should focus on drugs that can correct the abnormal immune response of RA, thereby interrupting the pathological process but avoiding toxicity for prolonged treatment. Chinese medicine can effectively balance the ratio of pro-inflammatory to anti-inflammatory cytokines, a mechanism that requires further research. At the same time, combined with evidence-based medicine, further research may help to clarify the mechanisms of regulation that how Chinese medicine treatments adjust cytokines. Finally, we expect to obtain an ideal treatment that can control the progress of RA, prevent joint tissue destruction and deformity, and maintain joint function.

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(Received May 6, 2012)
Edited by WANG Wei-xia