

## Review

# A review of inflammatory signaling pathway regulated by acupuncture \*

## 针灸调控炎症通路相关研究的回顾\*

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### ABSTRACT

**Objective** To analyses the studies about acupuncture regulating inflammatory signaling pathway in treatment of inflammation-related diseases, which can explain the possible mechanism and provide evidence of acupuncture in treatment of inflammatory diseases. **Methods** Acupuncture-related studies of animal experiments and clinical trials in PubMed about three signaling pathway, Janus protein-tyrosine kinase/signal transducer and activator of transcription (JAK-STAT), nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) were retrieved. The effective of acupuncture on cytokines of the three signaling pathway were analyzed and systematically summarized. **Results** Acupuncture can inhibit the activity of JAK-STAT, NF-κB and MAPK inflammatory signaling pathway by down-regulate the cytokines of them. **Conclusion** Acupuncture and moxibustion have the function of anti-inflammation though inhibiting the JAK-STAT, NF-κB and MAPK signaling pathway. Anti-inflammation maybe plays a vital role in the mechanism of acupuncture and moxibustion.

**KEY WORDS:** acupuncture; inflammation; JAK-STAT; NF-κB; MAPK

Traditional Chinese acupuncture which is defined as needling insertion, moxibustion stimulation at acupoint, had been accepted by all over the world for its effectiveness and simplification in recent decades. In addition to its widespread application for the treatment of pain<sup>[1-4]</sup>, acupuncture had been used to treat a variety of inflammatory diseases including asthma, rhinitis, inflammatory bowel disease and peripheral joint osteoarthritis<sup>[5-8]</sup>. Increasing evidences also demonstrated that electroacupuncture (EA) significantly inhibits the inflammatory response in mouse models of inflammation induced by several signaling pathway.

The Janus protein-tyrosine kinase/signal

transducer and activator of transcription (JAK-STAT), nuclear factor kappa B (NF-κB) and Mitogen-activated protein kinase (MAPK) are three important cellular signaling pathways, which played pivotal roles in regulation of cellular physiologic as well as pathophysiologic functions. These three signaling pathways participate in inflammatory action though varies cytokines such as TNF-α, IL-1, IL-6. The induction, influence and inflammatory effect of cytokines are closely related to the three signaling pathways. Studies about underlying mechanism of acupuncture and inflammation signaling pathway were performed for several years. The review focuses on the possible mechanism of acupuncture and moxibustion regulated in the three inflammation signaling pathway.

## JAK-STAT PATHWAY

JAK-STAT is one of the main pathways downstream of cytokine receptors and growth factor receptors by transducing signals from cell surface to the nucleus, which involves in the process of cell proliferation, differentiation, apoptosis, migration and immune regulation. Proved in lot of studies<sup>[9-11]</sup>, JAK/STAT pathway is closely related to inflammation. Besides controlling its downstream inflammation related gene expression, JAK/STAT pathway also connects with other inflammation signaling pathway including NF- $\kappa$ B, which plays a critical role in the part of inflammation. Studies of acupuncture and moxibustion in regulating JAK/STAT pathway are focus on the inflammatory disease including rheumatoid arthritis (RA), cerebral ischemia and knee osteoarthritis. YANG<sup>[12]</sup> tested the expression of Suppressor of cytokine signaling 1 (SOCS1), Suppressor of cytokine signaling 3 (SOCS3) which are the suppressor of cytokine signaling proteins in JAK-STAT pathway of synovium cells in RA rabbits. The results showed that comparing to normal control group, synovial SOCS 1 and SOCS 3 expression levels were remarkably higher in the model group and moxibustion group. The expression obviously decreased after moxibustion group compared with the model group. The perimeters of bilateral knee joints in the moxibustion group were significantly decreased, suggesting an improvement on the inflammatory reaction after moxibustion intervention. The author suggested that moxibustion intervention has an anti-inflammatory and detumescent effect in RA rabbits, which may be closely associated with its effects in down-regulating expression of SOCS 1 and SOCS 3 proteins by suppressing negative feedback regulatory JAK/STAT pathway in synovial cells. Additionally, YANG<sup>[13]</sup> analyzed the expression of signal molecules associated with JAK-STAT pathway with gene chip and bio-information analytical techniques, and observed the effect of moxibustion on JAK-STAT pathway of synovial cells in RA rabbits. The results showed that compared with control group, JAK-STAT pathway-associated genes with up-regulated expression in model group were C/EBP beta, CBP, CRP, GATA3, IFNAR1, IFNAR2, IFNGR2, IL-10Rb, INDO, SH2B, STAT3, STAT6, JAK3 and GP130, and those with down-regulated expression were A2M, MIG and IL-2Rr, suggesting an abnormal activation of JAK-STAT pathway; while in comparison with model group, the related gene up-regulated in moxibustion group in the expression was IL22R and those down-regulated were Cyclin D1, C/EBP beta, CRP, GATA3, IFNAR2, INDO, JAK2, JAK3, V-JUN,

STAT3, STAT5, SH2B and OSM, which showing that moxibustion had an apparent inhibitory effect on AR-induced abnormal activation of some genes as C/EBP beta, GATA3, IFNAR2, INDO, etc. Moxibustion can resist inflammation and eliminate swelling in RA rabbits, which may be closely related with its effect in inhibiting abnormal activation of JAK-STAT pathway in synovial cells. LIU<sup>[14]</sup> observed the expressions of Janus kinase 2 (JAK2) mRNA and phosphorylated JAK2 (p-JAK2) in the ischemic cortex of rats. The results showed that EA treatment was able to improve the neurological deficit score after cerebral ischemia, and down-regulate the expressions of JAK2 mRNA and JAK2 phosphorylation, which suggested the therapy of EA could reduce the expression of JAK2, and inhibit JAK2 phosphorylated activation, so as to block the abnormal activation of signal transduction pathway which was induced by JAK2 in JAK-STAT pathway. There are also some scholars<sup>[15]</sup> that have detected effect of warming-needling therapy on the gene expression pathway including JAK-STAT in the patients with knee osteoarthritis. The results showed that JAK-STAT related genes were up regulated. Authors suggested that Stats lead lymphocyte and synovial fibroblasts apoptosis, which protect the procedure of osteoarthritis occurred. This results of gene chip technology were not correspond with other studies, which reason may be related with the test methods. Furthermore, different manipulation methods of acupuncture would have various effect of human. Liu<sup>[16]</sup> detected the binding ability of signal transducers and activators of transcription (STAT5) in human peripheral blood mononuclear cells (PBMC) with DNA. The results showed that the reinforcing manipulation methods could increase the basic transcription level of STAT5 mRNA in human PBMC and the binding ability of STAT5 with DNA significantly. Inversely, the reducing manipulation method did not have significantly changes as compared with those in the normal control group. All of the studies suggest that acupuncture and moxibustion could regulate the pathway of JAK-STAT and has the function of anti-inflammatory. All the results of studies mentioned above are summarized in Table 1.

## NF- $\kappa$ B PATHWAY

The nuclear factor kappa B (NF- $\kappa$ B) regulates the expression of genes controlling the immune and stress responses, inflammatory reaction, cell adhesion, and protection against apoptosis. It is composed of five proteins belonging to the Rel family. The most extensively studied signals are tumor necrosis factors (TNF), interleukin-1 (IL-1) and Toll-like receptor (TLR), which are the upstream of the NF- $\kappa$ B pathway.

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