

Exploring New Therapeutic Approaches for Rheumatoid Arthritis Based on Basic Signaling Pathways

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Abstract. RA is an incurable systemic inflammation the main features are infiltration of pro-inflammatory factors with joint swelling and pain as the main clinical manifestation. Studies have shown that there are many causes of RA, among which immune factors are the most important pathogenesis of rheumatoid arthritis. At present, emerging studies have found that PI3K / AKT / mTOR signaling axis is abnormal in patients with RA, which opens up new ideas for the treatment of RA through the normal expression of signal transduction by targeted drugs. Janus kinase family (JAKs), are up-regulated in non-receptor protein tyrosine kinase cytokine signaling (SOCS) inhibitors, suggesting that the existence of SOCS is most possibly to constitute the main machine-made of negative adjustment of JAK / STAT signaling. In RA patients, there is a correlation between the activation of mTOR signaling and the quantity of osteoclasts. The recently discovered cytokine IL-22 has been shown to significantly increase the number of fibroblasts isolated from the skin of the patients with psoriasis. The dual inhibitor of P1-3K / mTOR, NVP-BEZ235, effectively blocks the spread. This article mainly explores and discusses new targeted drugs such as tofacitinib and Ruxolitinib by discussing new pathological mechanisms and conventional diagnosis and treatment methods of RA. Since RA is one of the most representative diseases of skeletal immune diseases, the study of ra abnormal signaling pathways to discuss related treatment methods provides valuable insights into the disease and other inflammatory and autoimmune diseases.

Keywords: Traditional treatment methods for RA; New treatment methods for RA; Signal path.

1. Introduction

Rheumatoid arthritis (RA) is a diffuse, inflammatory cytokine infiltrating, symmetric, slowly developing inflammatory autoimmune disease that can affect the whole body. The main clinical manifestations are joint fever, swelling, numbness, and pain, accompanied by subcutaneous nodules, dry eyes, dry mouth, and partial diarrhea. After the onset of the disease, the heart, blood, lungs and kidneys may be involved, and the tendons and ligaments will become fragile accordingly. The global prevalence of RA was about 0.24 %. Gender and age also lead to differences in prevalence. Women (3.6 %) are about twice as likely as men (1.7 %). The risk of RA also increases with age, and the incidence rate peaks between 65 and 80 years old [1].

Previous studies have shown that RA is a combination of genetic and environmental influences on patients. In national academic research of 91 MZ and 112 DZ pairs in the UK, the total MZ agreement rate was 15 %, while the twins were 5 %. Seropositive RA's heritability is about 40 % ~ 65 %, and the heritability of seropositive RA is about 20 % [2]. Polymorphisms, including HLA-DRB1 alleles, PAD14, PTPN22, CTLA4, CCR6 and IRF5 and so on, may also increase the prevalence of RA [3,4]. In terms of environmental factors, smoking, respiratory dust and obesity have become the triggers of RA. These factors also indicate that contact with various antigens outside the host site far from the joint will trigger inflammatory reactions in joints. In addition, places including the lungs, oropharynx, and gastrointestinal tract can also be affected.

Because the causes of RA are diverse and complex, it is very helpful to clarify the underlying pathogenesis under the etiology. At present, emerging studies have found abnormal PI3K / AKT / mTOR signaling axis in RA patients, which opens up a new idea for the treatment of RA by targeting the normal expression of drug signal transduction [5]. This review will discuss the study of abnormal signaling pathways that induce RA and the corresponding treatment methods. As the most representative skeletal immune disease, the study of RA can provide important insights into other inflammatory and autoimmune diseases.

2. The pathogenesis of RA

There are many different and intricate processes that contribute to RA, including stromal, innate, and adaptive components that also have an impact on the disease's systemic symptoms. There is still much to learn about the exact pathophysiology and etiology. Nonetheless, it is recognized that bone marrow cells, particularly macrophages, are crucial to the ongoing pathogenesis of illness [6].

The typical monofilm synovial membrane becomes hyperplastic in the synovial joint of RA. This transformation happens as a result of immune and non-immune cells that have been activated migrating and adhering more actively, assisted by increased amounts of certain chemokines and adhesion proteins. These processes are influenced by a variety of substances, like interleukin and others [7]. Expression of the gene for A Disintegrin And Metalloproteinase (ADAM) and general alterations in RA synovial joints brought on by a number of causes, such as inhibition of chondrogenic extracellular matrix production, increased frequency of apoptotic chondrocytes, "apoptotic resistance" in synovial tissue, increased expression levels of matrix metalloproteinase (MMP) genes, are both important aspects of the RA process [8]. Recent studies indicate that proinflammatory cytokines' stimulation of the JAK/STAT signal transduction pathway is an important point in progress of RA. Cytokine signal inhibitor and activated STAT protein inhibitor are two examples of JAK/STAT negative regulators [9]. Both regulators, though, are not working properly in RA. As a result, continuing JAK/STAT signalling activation in the synovial joints of RA patients increases the expression of the matrix metalloproteinase gene and the frequency of apoptotic chondrocytes [9].

3. Conventional treatment of RA

RA is an incurable chronic inflammatory autoimmune disease which characterized by diffuse, symmetrical polyarthritis, erosive and proinflammatory cytokine infiltration [10]. The main clinical manifestations are joint fever, swelling, numbness and pain, accompanied by subcutaneous nodules, dry eyes and dry mouth, and some diarrhea. It may involve the heart, blood, lungs and kidneys. The main early onset of RA is seen in joint stiffness, swelling and tenderness. After the occurrence of the lesion, joint deformity and peripheral muscle atrophy will occur. Therefore, the focus of diagnosis and therapy is to relieve arthrosis ache and tumidness, against joint deformity, control the disease process and ensure the improvement of patients' quality of life. The treatment of RA mainly includes medication, physical rehabilitation, surgical intervention and health education. The cure of RA mainly depends on the drug use, through the selection of anti-rheumatic drugs to alleviate the disease.

3.1. Drug Therapy

The symptomatic treatment of RA mainly includes DMARDs, NSAIDs and GCs, but after accurately assessing the benefit-risk balance, weak opioid analgesics can also be considered for short-term pain treatment.

3.1.1. DMARDs

Studies have shown that anti-rheumatic drugs (DMARDs) can effectively control the systemic spread of the illness, delay the progression of the disease and alleviate the adverse reactions caused by the disease. Methotrexate is the preferred drug for RA's healing [11]. Methotrexate was first created in 1947 as a drug for the cure of cancerous diseases. Later, it was found that low-dose

methotrexate could be used as a safer and well-tolerated drug for the therapy of some autoimmune illness, and then low-dose methotrexate became the first-line drug for RA. Methotrexate is a synthetic compound that reduces the content of tetrahydrofolate that can be used in cells by inhibiting dihydrofolate reductase, affecting the metabolism of pyrimidine and purine, resulting in blocked DNA synthesis [12]. RA is mainly caused by inflammatory cell infiltration and the release of inflammatory mediators, and methotrexate can alleviate the inflammatory process of RA by inhibiting the proliferation of inflammatory infiltrating cells. Methotrexate is used to treat RA with 7.5mg-15mg per week, mainly in small doses.

Table 1. Several other common DMARDs in China

Targeting DMARDs	the mechanism of drug	medication method
tumor necrosis factor alpha inhibitor	By binding tumor necrosis factor, blocking the signal transduction of immune cells, inhibiting the activity, regulating the inflammatory response of RA.	Injections are given according to individual differences
Interleukin (IL) -6 receptor antagonist.	It inhibits the inflammatory response of RA by specifically binding to the soluble nuclear membrane binding IL-6 receptor.	The common dose is 8mg / kg, intravenous infusion once every four weeks.
T cell costimulatory signal modulator	Block the second signal required for T cell activation, inhibit T cell activation, and treat RA inflammation.	The common dose is 125mg / week, subcutaneous injection.
anti-cd20 monoclonal antibody	Inhibition of autoinflammatory response by inhibiting B cells	It is recommended to measure 1000 mg each time, intravenous drip once on the first day and the fifteenth day (allergic reaction test before use).
Biosimilar DMARDs	/	Use according to individual differences.
Janus kinase inhibitor	Treatment of RA by inhibiting inflammatory factors dependent on JKA pathway	The common dose of tofacitinib was 5 mg each time, twice a day. Baretinib 2-4 mg each time, once a day

3.1.2. NSAIDs

The main clinical manifestation of RA is ache. Prostaglandin is a very important inflammatory substance that causes pain. Binding to the corresponding receptor will produce a pain signal to the brain, and cyclooxygenase is a key rate-limiting enzyme for prostaglandin synthesis. The main mechanism of NSAIDs is to reduce the synthesis of prostaglandins by inhibiting the activity of cyclooxygenase to inhibit the release of inflammatory mediators and relieve the pain caused by RA. In the pathogenesis of RA, cyclooxygenase-2 is the main component of prostaglandins involved in the synthesis of pathological processes, while cyclooxygenase-1 has the effect of protecting the endothelium of gastric mucosa and other organs.

Traditional non-steroidal anti-inflammatory drugs (mainly ibuprofen, aspirin) can inhibit cyclooxygenase-1 and cyclooxygenase-2 at the same time, and have anti-inflammatory and analgesic effects, but they can significantly stimulate gastric mucosa and cause gastric mucosal damage [11]. Excessive use can cause upper gastrointestinal bleeding, patients will have a series of adverse reactions, and NSAIDs will also cause cardiovascular and cerebrovascular adverse reactions. Therefore, NSAIDs are not the first choice in the treatment of RA.

3.1.3. GCs

GCs are a class of steroid hormones secreted by the zona fasciculata in the adrenal cortex, which have a rapid, powerful and non-specific anti-inflammatory effect. In the early stage of inflammation, it can inhibit the expansion of capillaries, reduce the exudation and edema of body fluids, thereby inhibiting the phagocytosis and infiltration of white blood cells and alleviating inflammation [13]. It can also inhibit arachidonic acid metabolism to reduce the synthesis of leukotrienes and prostaglandins, thereby reducing the inflammatory response and relieving pain, and can quickly improve joint swelling and systemic symptoms. Compared with NSAID, GCs have better efficacy but greater side effects, including diabetes, osteoporosis, immunosuppression, etc. Therefore, the principle of GC use is to use small doses of short courses, and to supplement calcium and vitamin D in a timely manner during treatment.

3.2. Interventional Surgery

For patients with advanced RA, the main symptoms of RA in this period are joint deformity, most commonly in subluxation of both hands and ulnar deviation. Patients in this period often have joint deformity, joint deformity and joint movement disorders [10]. Drug therapy has been unable to meet their needs to alleviate the condition. At this time, surgery has become the first choice. The surgical treatment of RA is mainly reflected in joint replacement and synovial cleaning. Common RA surgical interventions include synovial resection, artificial joint replacement, joint fusion and other surgical forms to remove pathological lesions, improve the patient's condition, and alleviate the progression of RA.

Artificial knee arthroplasty is mainly to replace the damaged bone on the surface of the knee joint with an artificial prosthesis, remove the worn area, and inlay an artificial prosthesis on the surface to alleviate the friction between the bones and enable the patient to move normally. TKA can effectively avoid the adverse consequences caused by long-term bedridden patients. It is the first choice and the best choice for patients with end-stage RA, and there are many options for knee prosthesis at present. However, TKA requires high surgical costs and may not meet the high expectations of patients after surgery. Therefore, surgery is not a priority for RA patients.

3.3. Physical rehabilitation therapy

The physical rehabilitation treatment of RA mainly includes acupuncture, massage and moxibustion in traditional Chinese medicine. Through the stimulation of acupoints and meridians, combined with massage, it can relieve the pain of peripheral muscle atrophy and joint swelling caused by RA, stimulate blood circulation and prevent subcutaneous masses. Physical rehabilitation of RA mainly includes cold / heat therapy, electrical stimulation therapy and exercise training.

3.3.1. Cold / heat therapy

Pain can easily lead to muscle contracture, motor dysfunction and limited daily activity, so pain treatment is very important. The acute phase of RA was treated with cold compress, while the chronic phase was treated with hyperthermia. Hyperthermia mainly uses surface hot compress, infrared radiation, paraffin, liquid therapy or hydrotherapy to relieve pain and spasm, promote blood flow and tissue repair. Cold therapy mainly uses cold compress, ice compress, nitrogen spray and cryotherapy to relieve inflammation and pain in the acute phase.

3.3.2. Electrical stimulation therapy

Electrical stimulation therapy for RA mainly uses TENS therapy. The mechanism of TENS is to inhibit the transmission of pain impulse at the level of spinal cord glia and more concentrated changes in pain perception. Relevant research shows that another possible mechanism is the release of opioid drugs in the body [14].

TENS therapy can not only be used for analgesia, but also has a good effect on improving peripheral blood circulation and promoting soft tissue regeneration. The frequency is positively

correlated with the effect, with abirritation lasting up to 18 hours [15]. Using TENS for 3 weeks(once a week), the pain will be reduced [16]. And it also has a high placebo effect.

3.3.3. Sports training

Exercise training is an effective adjunctive therapy to enhance the cardiopulmonary function of RA patients. In addition to drug therapy, specific exercise therapy may reduce heart and lung diseases associated with RA.

In order to prevent spasm and adhesion of joint soft tissue, it should be ensured that each arthrosis should be moved at least once a day in ROM. The safest and most effective type of exercise for RA patients is low intensity iso kinetic knee exercises [17]. If there is pain or excessive tired, loss of power or increased swelling of joint when after exercise, the training plan should be modified in time. At the same time, it is recommended to carry out regulatory soothing exercises such as swimming, walking and Taijiquan, and have enough rest time.

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3.4. Patient health education

For patients, in addition to physical pain, the disease will also bring psychological pressure. While treating and rehabilitating patients, we should not only explain the relevant disease knowledge and treatment plan for patients, but also pay close attention to the mental health of patients, timely relieve patients, reduce the psychological pressure of patients, and give patients psychological support to increase patients ' confidence in the treatment plan and promote patients to alleviate the disease.

Because of the large side effects of GCs are immunosuppression, methotrexate and NSAIDs are mainly used as the first-line clinical drugs [12]. Physical therapy mainly uses TENS and cold and hot therapy to relieve pain and muscle spasm, and even play a placebo effect. In the middle and late stage of RA, surgical intervention is adopted. According to the different diseases of patients, synovectomy or joint replacement is adopted to maintain the normal function of joints, reduce pain and improve the ability of daily life. It should be emphasized that after prevention and surgical treatment, it is recommended to take palliative measures. Electrotherapy, cold and hot therapy and acupuncture and moxibustion and massage require patients to be treated in the hospital on time for a long time, which is inconvenient for most patients, and the treatment process is long, So it is recommended that patients take medication.

4. New therapeutic

4.1. Tofacitinib

Tofacitinib is suitable for the treatment of methotrexate deficiency in patients with moderately active RA. In one example, Lee's group tested 958 patients who took tofacitinib or methotrexate for six months to see if there was a significant reduction in joint swelling. The results showed that tofacitinib (>50%) was better than methotrexate (12%) [18]. Many RA patients who participated in the study met the American association of rheumatism -20 (ACR20) response standard at week 2 and also achieved at week 24. It has also been proven to have a long-term effect of 4 years in patients with RA [18]. Currently, different clinical trials indicate that the incidence of clinical adverse events, including major cardiovascular, severe infection, opportunistic infection, tuberculosis, deep vein thrombosis, gastrointestinal perforation, tumor, death and other serious adverse events after treatment with JAK inhibitor tofacitinib, is very low, which is basically the same as the incidence of adverse events of antirheumatic drugs.

After multiple investigations in rats confirmed the efficiency of tofacitinib as an immune suppressant, Borie and his team recommended tofacitinib as a jak inhibitor to prevent transplant

rejection [19]. Thus, tofacitinib showed a good safety profile in nonhuman primates and dramatically increased allograft survival in a number of monkey investigations. JAK3, JAK2, and JAK1 were all found to be inhibited by tofacitinib. Tofacitinib was created by the gradual improvement of JAK3 inhibitors based on pyrrolopyrimidines [20]. Tofacitinib has been demonstrated to be effective in randomised clinical studies in individuals suffering from rheumatoid arthritis.

4.2. Ruxolitinib

Ruxolitinib is a JAK1/JAK2-selective Jakinib that has been authorised for the treatment of psoriasis and myeloproliferative disorders [21]. According to Gadina, creating JAK SMIs that target multiple JAKs does not appear to be "difficult" on the surface [22]. In a Williams and colleagues' randomised clinical trial with active RA patients, 33% of those receiving ruxolitinib met the ACR70 response criteria, compared to 0% in the placebo group [23]. The most common adverse reactions of this drug are anemia, thrombocytopenia, dizziness and headache. Ruxolitinib is a JAK inhibitor. At present, ruxolitinib is mainly used in the treatment of myelofibrosis (MF). Although it has clear benefits in the treatment of MF, the diagnosis and management of RA are still in the theoretical stages. The efficacy and safety of its clinical treatment still need long-term further research experiments [24].

At the pathophysiological level, CD-40, and IL-6 plasma levels were both decreased by ruxolitinib-mediated inhibition of JAK1/JAK2. Additionally, p-STAT3 was suppressed by ruxolitinib in an ex vivo study using RA patients' blood cells. Menet and coworkers confirmed that JAK1 was necessary for the common chain cytokines transduction and also the IL-6 signalling in this regard. [25].

5. Conclusion

Selecting therapies based on signaling pathways means that an immunotargeted approach are being used, representing a major advance in illness management. It is important to note that in addition to the JAK inhibitors mentioned here, TNF and IL-6 inhibitors are also particularly effective in providing a clinical response. However, the blocking of IL-17, IL-1, BAFF, IL-21 and IL-20 has not been found to be very effective. One of the benefits of using JAK inhibitors is that different drugs have different selectivity for different kinases, which can achieve better therapeutic effect for RA with complex etiology. They can play a special role in the early stage of these sickness, without waiting for obvious symptoms can be interventional treatment, can obtain a good prognosis. However, this approach has certain limitations that in the current study, in the treatment of RA, it may be necessary to only inhibit the activation of JAK/STAT, SAPK/MAPK, or PI3K/AKT/mTOR mediated by proinflammatory cytokines, but this cannot completely lead to clinical recovery.

Here, two new possible research directions are proposed: (1) Consider the development of new targets for intervention of abnormal enzyme activity against splenic tyrosine kinases, transforming growth factor β -activated kinase-1, sphingosine kinase-1, -2, bone marrow kinase, and nuclear factor κ B-induced kinases. (2) Consider the combination of signal inhibitors and other drugs for better efficacy.

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