

Advancements in Targeted Therapy for Rheumatoid Arthritis

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Abstract:

In recent years, the treatment of rheumatoid arthritis has broadened the variety. In particular, targeted therapy has become the most concerned treatment. Many of the shortcomings of traditional treatment modalities, such as expensive drugs and severe side effects, can be replaced by targeted therapy. Targeted therapy has not been widely used in clinical treatment, but it has been well understood and studied for many years. At the same time, many kinds of targeted drugs have been studied for the treatment of RA. This article analyzes the direction of several targeted therapy and drug research, about their different use methods, pathways, etc., and some are still under study. There are many research results, successful clinical trials, and significant improvement compared with traditional treatment. It can better treat patients and take care of their physical and mental health. Targeted therapy provides a reference for the subsequent research on the treatment of RA, and is also an excellent improvement of the treatment, but more clinical trials are still needed to truly popularize a variety of targeted therapy to patients.

Keywords: Targeted therapy; rheumatoid arthritis; clinical trials.

1. Introduction

Rheumatoid arthritis (RA) is a chronic disease that causes systemic inflammation, usually manifested as joint pain. Untreated RA causes severe damage to joints and their surrounding tissues. It can even cause problems in the heart, lungs or nervous system. Common symptoms include chronic pain, stiffness, tenderness, fever and swelling in the joints. RA can make mobility and daily activities difficult. The etiology of RA is unknown. Risk factors include smoking, obesity, and exposure to air pollution. The risk of RA is higher in women and the elderly [1]. There are several anti-arthritis drugs currently on the market, most of which are relatively expensive, have limited efficacy, or have unavoidable side effects. Non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), disease-modifying antirheumatic drugs (DMARDs), and biologics are widely used in the treatment of rheumatoid arthritis. Nsaid-induced nephrotoxicity, liver injury, and heart failure are all potential side effects of these treatments, despite their ability to slow disease progression. If medical treatment is still ineffective, the only other option is surgery [2]. Due to the complexity of the pathogenesis and pathophysiology of RA, there is also an urgent need to adopt new technologies to develop a new treatment that can overcome the persistent inflammation of RA [3]. Many studies have shown that chemically modified siRNA targeting signaling pathways

may be a potential treatment for RA. Activated fibroblast-like synoviocytes (FLSs) are the main cell type in the proliferative synovial lining of RA, which play an important role in synovial membrane formation and joint injury. Proliferation, apoptosis resistance, and enhanced invasiveness are hallmarks of the aggressive phenotype of RA-FLS, leading to angiogenesis and bone erosion. Targeted activation of RA-FLSs is an attractive and promising treatment for RA [3]. There are also other examples such as efficient delivery of DSP and plasmids into cells through targeted drug delivery systems [4]. In order to achieve the effect of targeted drug delivery, nanotechnology can be used. Many researchers have been working to develop various nanoparticle systems for the treatment of RA by directly or indirectly targeting the information domain. Improved bioavailability, targeting, and enhanced therapeutic effects are major advantages of these systems [2]. In recent years, nanoparticles (NPs), as a new drug delivery system, have been applied to the targeted therapy of RA. By loading small molecule drugs or cell surface molecular inhibitors with controllable nanomaterials, the nano-drug delivery system can specifically target the drug to regulate the disordered immune system of RA or block the abnormally activated signaling pathway transduction pathway to effectively control the development of the disease. It alleviates clinical symptoms and overcomes the toxic side effects caused by the distribution of conventional drugs in normal tissues [5,6]. As a new drug delivery

system, targeted therapy has not been widely used in the clinical treatment of RA. This article briefly introduces the molecular mechanism of RA pathogenesis, and reviews several representative types of targeted therapy commonly used in recent years, so as to provide theoretical basis for the innovation and development of RA treatment methods and promote the implementation of precise targeted therapy for RA patients.

2. Pathogenesis of RA

2.1 Background of RA

The important fact is that until 2019, 18 million people worldwide had RA. Approximately 70% of RA patients are female and 55% are over 55 years of age. 13 million patients had RA severity (moderate or severe) that could be improved with rehabilitation. Although RA is a systemic autoimmune disease that affects multiple systems of the body, the joints of the hands, wrists, feet, ankles, knees, shoulders, and elbows are most commonly affected. RA is a highly heterogeneous autoimmune disease characterized by local synovial cell infiltration and bone erosion in the joint cavity. The main pathological changes are progressive joint inflammation and cartilage tissue destruction caused by immune system disorders, and extra-articular systems are often involved in the course of the disease [6]. The disease is commonly seen in adults in their 60s. Women are two to three times more likely to be affected than men. The prevalence of RA is higher in industrialized countries, which may be due to demographics (higher average age), exposure to environmental toxins and lifestyle risk factors, and underdiagnosis in low - and middle-income countries [1].

2.2 Pathogenesis and Symptoms of RA

RA is a chronic synovial inflammation of the affected joint. Its pathological mechanism is related to various cells such as T cells, B cells and FLS, as well as interleukin (IL) -1 and tumor necrosis factor α (TNF- α) and other inflammatory cytokines act together to produce autoantibodies against the autoantigen (collagen type II of articular cartilage), which eventually leads to synovial inflammation and bone and cartilage destruction [7]. RA causes inflammation and pain in one or more joints. „It can occur in most joints, but is most commonly found in the small joints of the hands, wrists, and feet.“

RA is chronic and may worsen over time if left untreated. It can cause severe damage to the joints and their surrounding tissues. It also affects the heart, lungs and nervous system. Early signs and symptoms include pain, stiffness, tenderness, swelling or redness in one or more joints, usually symmetrical (for example, both hands or

feet). Symptoms can worsen over time and spread to more joints, including the knee, elbow, or shoulder. RA severely affects People's Daily life and can make daily activities (such as writing, holding objects with their hands, walking and climbing stairs) difficult. People with RA often experience fatigue and general malaise (e.g., fever, poor sleep quality, loss of appetite) and may present with depressive symptoms. Pain and mobility difficulties can lead to problems with sexual functioning and intimate relationships. Reduced mobility can lead to reduced physical fitness, loss of independence, inability to work, reduced well-being and mental health problems [8].

3. Development of Targeted Therapies

3.1 Development of New Targets

Nanotechnology has revolutionized every area of applied science. Nanoparticle systems have attracted much attention due to their potential to explore drug-loaded nanoformulations of various anti-inflammatory drugs [9]. Some reported nanoparticle systems for the treatment of RA are included. Many researchers have been working to develop various nanoparticle systems for the treatment of RA by directly or indirectly targeting the information domain. Improved bioavailability, targeting, and enhanced therapeutic effects are major advantages of these systems. The PEGylated nanoparticle system can prolong the circulation time. In addition, the system can also be used to develop new targets, and smart nanojoint systems have been designed to release therapeutic drugs only when a trigger or stimulus is encountered. The delivery and treatment methods of this new target are divided into passive targeting and active targeting. Passive targeting mainly depends on EPR effect. EPR effect refers to the high permeability and retention effect of solid tumors, which refers to the phenomenon that some macromolecular substances of specific sizes, such as liposomes, nanoparticles and some macromolecular drugs, are easier to penetrate into tumor tissues and retain for a long time. Angiogenesis is critical in chronic inflammatory diseases such as RA because of local hypoxia and growth factor production in embedded joints. Active targeting after system delivery can be achieved by nanocoating connected systems with target parts. As the disease progresses, angiogenesis and inflammation are the most prominent features. Growth factors, cytokines, adhesion molecules, and proteases are all involved in the formation of angiogenesis in a variety of ways. Vascular endothelial growth factor (VEGF) and angiopoietin play a key role in the hypoxia-VEGF system. Multiple adhesion molecules were also overexpressed on the endothelial cell surface, including integrin $\alpha_3\beta_1$, E-selectin, vascular cell adhesion molecule 1 (VCAM1), and

intercellular cell adhesion molecule 1. The intercalated synovium is rich in macrophages and has a wide range of proinflammatory properties, contributing significantly to inflammation and joint damage. It is selected by binding to a specific receptor

Selective delivery of nanomedicine can close their complex connections with other cells and improve the RA state, as well, It retains the basic functions of resting macrophages [2].

3.2 Nano-targeted Pharmaceuticals

FLSs are the main cell type in the proliferative synovial lining of RA and play an important role in synovial membrane formation and joint damage. Proliferation, apoptosis resistance, and enhanced invasiveness are hallmarks of the aggressive phenotype of RA-FLS, leading to angiogenesis and bone erosion [10]. Targeted activation of RA-FLSs is an attractive and promising treatment for RA [11]. The hedgehog signaling pathway is a conserved pathway that plays a key role in embryonic development. In mammals, Hedgehog ligands interact with the transmembrane receptor patch 1 and alleviate the inhibition of smooth (SMO). Subsequently, a signaling cascade leads to the activation and nuclear trans-localization of glioma-associated oncogene family zinc fingers 1-3 (GLI1-3) [12]. GLI acts as a transcription factor, It drives the expression of target genes involved in pathway feedback regulation (PTCH1, PTCH2, GLI1), proliferation (CCND, CCNE, MYC), survival (BCL2), angiogenesis (ANG1/2, VEGFA), and epithelial-mesenchymal transition (SNAI1, TWIST1). Hedgehog signaling is normally quiescent in healthy adult tissues. In the occurrence and metastasis of various malignant tumors, including basal cell tumors, prostate cancer, myelocytoma, prostate cancer and prostate cancer, prostate cancer, Hedgehog signaling pathway, colorectal cancer and liver cancer [13]. In addition, Hedgehog signaling pathway has been found to be abnormally activated in rheumatic diseases such as RA, osteoarthritis, ankylosing spondylitis, and systemic sclerosis. 14 Considering these findings, inhibition of hedgehog signaling may contribute to the treatment of various cancers and inflammatory diseases. Currently, several small molecule antagonists of SMO, such as vismodegib, sonidegib, and glasdegib, have been approved by the US Food and Drug Administration (FDA) for the treatment of body-heart cuboid and AML [14]. However, systemic administration and the side effects of SMO resistance mutations have limited the therapeutic utility of antagonists, stimulating the exploration of new therapies [15]. Because small interfering RNA (siRNA) can mediate targeted mRNA degradation in a sequence-specific manner, it may be a selective method to interfere with the expression of target genes [16].siRNA

therapy is emerging as a potential and popular area of new drug development. However, because drug carriers are readily enriched in the liver and spleen, all approved siRNA drugs target only liver disease. Successfully stabilizing siRNAs and efficiently delivering them to target tissues has become a challenge for the therapeutic application of siRNA drugs. Accumulated evidence suggests that chemical modifications make it possible to improve the performance of siRNAs. Appropriate modification of siRNA can improve its effectiveness, specificity, and characterization while minimizing its biotoxicity and immunogenicity [17]. In addition, local administration facilitates delivery of siRNA to intended tissues other than the liver and reduces unintended organ side effects [18]. Therefore, intra-articular injection of chemically modified anti-SMO-siRNA may be a potential treatment for RA.

3.3 Multiple Directions of Targeted Therapy

There are multiple directions for targeted therapy of RA. Some cutting-edge technologies for RA treatment are emerging, such as: Targeted protein degradation is used as a new treatment method to solve diseases caused by abnormal expression of pathogenic proteins by using protein degradation targeted conjugate (PROTAC) technology. PROTAC molecules can bind E3-ubiquitin ligase and target proteins at the same time, resulting in ubiquitination and degradation of target proteins [19]. However, the delivery and bioavailability of PROTAC remain the biggest obstacles to clinical application [20]. Addressing these questions will be the focus of research in many laboratories in the coming years. Protac-mediated JAK degradation has been proposed as a novel and promising treatment strategy for RA [21]. In addition, nanoparticle drug delivery systems, CRISPR-Cas9 genome editing technology and other technologies have also been developed for RA treatment.

3.4 Differences between Targeted Therapy and Usual Treatment

In the treatment of RA, the common treatment is to take anti-inflammatory drugs or traditional Chinese medicine (TCM) therapy. There are several anti-arthritis drugs currently on the market, most of which are relatively expensive, have limited efficacy, or have unavoidable side effects [2]. Anti-inflammatory drugs often have a great burden on the liver and kidney of the human body, and the side effects cannot be ignored. However, the long duration of TCM treatment often affects the patient's labor force and the efficiency of creating productivity.

With the introduction of new targeted drugs, the treatment of RA has entered the era of targeted therapy. New targeted drugs can quickly relieve symptoms, which is condu-

cive to early intensive treatment and treatment to target. Targeted drugs are fast and potent, continuously reach the target, multiple benefits, and are safe and economical. At the same time, a variety of targeted drugs are orally administered and have rapid onset of action. For example, oral administration of tofacitinib can be rapidly absorbed, and only needs to be taken twice a day. It can be stored and carried easily, and patients do not need to go to the hospital for injection, which can improve the treatment compliance of patients. In addition, it can take effect rapidly within two weeks, which greatly meets the treatment needs of RA patients and brings more clinical benefits to patients. More important, targeted therapy has few side effects.

3.5 Impact on Patients after Targeted Therapy

Targeted therapy can first reduce inflammation in patients, and targeted drugs can directly act on specific molecules that cause inflammation and reduce joint symptoms. Targeted therapy also improves the quality of life of patients by reducing pain and stiffness, improving joint function, and having a rapid effect. Targeted drugs can reduce the side effects of drugs, and compared with traditional non-targeted therapies (such as steroids and non-steroidal anti-inflammatory drugs), targeted therapy drugs usually have fewer side effects, which helps to reduce the overall drug burden of patients. Targeted therapy can choose appropriate drugs and doses according to the specific conditions of patients to achieve individualized treatment.

4. Conclusions

This article discusses the basic etiological mechanism and symptoms of RA, and mainly analyzes the advantages of targeted therapy, the mechanism of treating the disease, the types and targets of various targeted drugs, and the comparison of traditional treatment. This article explains the mechanism of RA in detail, and further analyzes the symptoms of RA according to its mechanism. The traditional treatment methods were compared with the new targeted therapy methods, and the methods of nano-targeted therapy were analyzed in detail. The main analysis is nanotargeted pharmaceuticals, as well as other targeted therapies. However, many targeted therapies, such as nano-targeted therapy, have not been formally applied to patients, and the clinical side effects of nano-targeted therapy have not been analyzed in this paper. Targeted therapy is still a very top technology in the medical field, and it will be better to treat patients after more stages of research. This is a great advance for the physical and mental health of patients, as well as a great advance in the medical research community.

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