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The role of TNF - α signaling pathway in rheumatoid arthritis and the therapeutic progress of TNF-α monoclonal antibodies

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Abstract:

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic synovitis and progressive joint destruction. Tumor necrosis factor - α (TNF - α) plays a central regulatory role in its inflammatory network. At present, biological agents such as TNF - α monoclonal antibodies (mAbs) have been widely used in clinical practice, significantly improving the prognosis of RA patients. But some patients have problems with poor treatment efficacy or infection. The differences and safety issues between different drugs still need further research. This article analyzes the immune imbalance mechanism of RA and the activation process of TNF - α signaling pathway, explores the mechanism of action and safety characteristics of TNF - α inhibitor drugs (adalimumab, infliximab, etanercept), and reviews the research progress of new inhibitors such as biosimilars. TNF - α inhibitors can effectively block downstream inflammatory signals and alleviate joint damage. However, there are significant differences in patients' response to treatment, and issues related to infection risk and immunogenicity limit the long-term use of drugs. This study provides a theoretical reference for investigating the mechanism of TNF - α targeted therapy for rheumatoid arthritis. At the same time, future research should focus on exploring biomarkers for predicting treatment response, optimizing individualized combination therapy, and developing new drugs for non-tumor necrosis factor pathways to cover a wider range of patients.

Keywords: Rheumatoid Arthritis; Cytokine; Monoclonal Antibodies.

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1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease. It is characterized by persistent synovial inflammation, progressive joint destruction and long-term disability. This disease affects about 0.5% to 1% of the world's population and poses a significant burden on public health [1]. The pathogenesis of RA involves the interaction between genetic susceptibility, environmental factors and immune disorders. Among various mediators involved, proinflammatory cytokines play an important role in disease progression.

A large number of studies have confirmed that tumor necrosis factor - α (TNF - α) is a key regulator in the inflammatory network of RA. TNF - α is mainly produced by activated macrophages and synovial fibroblasts, and is involved in local and systemic inflammatory reactions [2]. TNF - α activates downstream signaling pathways including nuclear factor kappa B (NF - κ b) and mitogen activated protein kinase (MAPK) by binding to TNFR1 and TNFR2 receptors, thus exerting biological effects. These pathways promote the transcription of pro-inflammatory genes and amplify the inflammatory cascade [3]. In addition, TNF - α can also stimulate the production of other cytokines, including interleukin-1 (IL-1) and IL-6, forming a cytokine network, thereby aggravating synovitis and joint injury [2].

Because TNF - α plays an important role in the pathogenesis of RA, the research and development of targeted biological agents have become the focus of attention. TNF - α inhibitors, especially monoclonal antibodies (mAbs), such as adalimumab and infliximab, and receptor fusion proteins, such as etanercept, have significantly improved the clinical treatment of RA [4]. These drugs block downstream inflammatory signals by neutralizing TNF - α or blocking its binding to cell surface receptors. There is clinical evidence that TNF - α inhibitors can effectively reduce disease activity, inhibit joint structure damage, and improve the quality of life of patients [5]. However, although it has therapeutic effect, it still has some limitations. These problems include individual differences in patients' response to treatment, increased risk of infection and immunogenic response.

It is precisely because TNF - α plays a central role in RA and TNF - α targeted therapy has been widely used. It is important to understand its basic mechanism and clinical progress. Therefore, this article aims to review the role of TNF - α signaling pathway in the pathogenesis of RA, clarify the mechanism of TNF - α monoclonal antibody, and explore the latest clinical progress, so as to provide theoretical reference for future research and treatment strategies. This review links the molecular mechanism of TNF - α driven inflammation with the therapeutic application of monoclonal antibodies in rheumatoid arthritis, with a focus on drug specificity differences and safety. This analysis provides a reference for understanding the variability of treatment response and guides future research on biomarker discovery and combination therapy optimization.

2. Pathogenic Mechanism of RA

2.1 The Role of Immune Disorders in Rheumatoid Arthritis

It is generally believed that rheumatoid arthritis (RA) is not caused by a single factor, but by a combination of multiple factors, including genetic susceptibility, environmental incentives and immune system dysfunction [1]. With the in-depth study of immunology, the central role of immune disorders in the pathogenesis of RA is gradually clear.

In the early stage of RA, abnormal activation of T cells is an important starting point for the induction of inflammatory response. Activated CD4+T cells can release a variety of pro-inflammatory cytokines, such as tumor necrosis factor - α (TNF - α), interleukin-17 (IL-17), interferon - γ (IFN - γ) [2]. These inflammatory mediators not only promote the activation of macrophages, but also stimulate the abnormal proliferation of synovial fibroblasts, leading to the continuous thickening of synovium and the spread of inflammation.

In addition to T cells, B cells also play an important role in RA. B cells are mainly involved in disease progression through autoantibodies, such as rheumatoid factor (RF) and anti citrullinated protein antibody (ACPA) [6]. ACPA is not only an important serological index of RA, but also closely related to the degree of bone erosion. Some studies even suggest that ACPA may be directly involved in the process of bone destruction, rather than just an "accompanying phenomenon" of disease activity. In addition, B cells can also activate T cells as antigen presenting cells, thereby further expanding the inflammatory response.

In conclusion, RA immune dysfunction is not caused by a single abnormal immune cell, but by multiple immune cells and inflammatory mediators, which provides a theoretical basis for the subsequent targeted therapy.

2.2 Inflammatory Cytokine Network

In the chronic inflammatory process of RA, the cytokine network is always in a state of continuous activation. Among them, TNF-α, IL-1, and IL-6 are considered to be the most critical pro-inflammatory cytokines. They pro-

mote and amplify each other, jointly maintaining synovial inflammation and joint damage [3]. Compared with the role of a single inflammatory factor, RA is more like a disease driven by a complex inflammatory network, so the synergistic effect between different cytokines is particularly important.

Among various inflammatory mediators, TNF-α is usually regarded as the "upstream regulator" in the inflammatory cascade. TNF-α is mainly produced by activated macrophages, T cells, and synovial cells. It can activate downstream signaling pathways such as NF - κ B and MAPK by binding to TNFR1 and TNFR2[3]. Subsequently, a large number of inflammation related genes were induced to express, including chemokines, adhesion molecules, and other pro-inflammatory cytokines, further exacerbating the local inflammatory response. Due to the upstream position of TNF - α in the inflammatory network, inhibiting TNF - α can usually simultaneously reduce the activity of multiple inflammatory pathways.

In rheumatoid arthritis (RA), interleukin-1 (IL-1) is more involved in cartilage destruction and synovial proliferation. For example, studies have found that IL-1 β can significantly promote the expression of matrix metalloproteinases (MMPs) in synovial fibroblasts, thereby accelerating the degradation of extracellular matrix in chondrocytes and promoting joint cartilage destruction [7]. The study by Arend et al. showed that IL-1 not only induces inflammatory responses, but also directly participates in the process of cartilage erosion. Therefore, IL-1 can be considered as one of the important mediators of joint structural damage in rheumatoid arthritis [8]. These findings indicate that the role of IL-1 in rheumatoid arthritis is not limited to amplifying inflammatory responses; It also has direct and indirect effects on joint tissue damage. Meanwhile, interleukin-6 (IL-6) is more closely associated with systemic inflammatory responses, such as acute phase protein synthesis, B cell differentiation, and abnormal bone metabolism. Therefore, although these inflammatory factors all have pro-inflammatory effects, their functions in RA are not entirely the same.

2.3 TNF-α Signaling Pathway Mechanism

TNF-α is a pro-inflammatory cytokine with broad biological activity, playing a key role in the inflammatory response and joint injury of RA [3]. Current research shows that TNF-α mainly exerts its biological function by binding to two receptors, TNFR1 and TNFR2. TNFR1 is widely expressed on the surface of various tissue cells and mainly mediates inflammatory responses and apoptosis; while TNFR2 is more distributed on the surface of immune cells and is closely related to immune regulation and cell survival [9].

When TNF-α binds to TNFR1, it can further recruit signaling proteins such as TRADD, TRAF2, and RIPK1, and activate downstream signaling pathways such as NF-κB, MAPK, and JNK [9]. Among them, the NF-κB signaling pathway is considered one of the important mechanisms for maintaining chronic inflammation in RA. When NF - κ B enters the nucleus, it induces the expression of IL-1, IL-6 and various chemokines, thus promoting the continuous infiltration of inflammatory cells and the amplification of inflammation. Compared with transient inflammatory stimulation, TNF - α signal in RA is often in a long-term abnormal activation state. This is an important reason for the difficulty of spontaneous remission of arthritis.

However, in recent years, some studies have shown that the role of TNF - α in different disease stages may not be completely consistent. For example, in some cases, TNFR2 may be involved in immune regulation and tissue repair [9]. It suggests that TNF - α signaling pathway is not a simple pro-inflammatory pathway, and its biological function may be more complex. Therefore, how to reduce the impact on normal immune function while inhibiting inflammation is the key problem of TNF - α targeted therapy.

3. Mechanisms and Differences of TNF-α Monoclonal Antibodies

3.1 Differences Between Different Drugs

At present, TNF-α inhibitors commonly used in clinical practice mainly include adalimumab, infliximab and etanercept. Although these drugs are targeted at TNF - α, there are some differences in their molecular structure, mode of administration, immunogenicity and clinical applicability. Therefore, when discussing TNF-α inhibitors in the paper, they should not be simply regarded as a completely identical class of drugs, but rather analyzed on a case-by-case basis for specific medications.

Adalimumab is a fully human IgG1 mAb. It can bind to soluble TNF-α and membrane-bound TNF-α, thereby blocking the interaction between TNF-α and its receptors. Due to its high degree of humanization, theoretically its immunogenicity is lower than that of chimeric antibodies, but it may still produce drug-resistant antibodies during long-term use, thereby affecting drug concentration and clinical efficacy. The PREMIER study conducted by Breedveld et al. showed that the combination of adalimumab and methotrexate was superior to methotrexate or adalimumab alone in improving clinical symptoms and inhibiting imaging progression in early and aggressive

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RA patients [10]. This study suggests that the therapeutic effect of TNF-α inhibitors depends not only on the drug itself, but also closely related to combination therapy strategies.

Infliximab belongs to the human mouse chimeric anti TNF-α mAb and is usually administered via intravenous infusion. Due to the presence of mouse derived components in its molecular structure, it is easier to induce the production of drug-resistant antibodies compared to whole human antibodies and may cause infusion reactions. Lipsky et al. found in the ATTRACT study that for RA patients with insufficient efficacy of methotrexate in the past, the combination of infliximab and methotrexate treatment can significantly improve clinical symptoms, physical function, and quality of life compared to methotrexate alone [11]. This result indicates that Infliximab has clear efficacy in the treatment of RA, but its clinical application often requires the combination of methotrexate to enhance efficacy and reduce immunogenicity risk.

Etanercept is different from the two mAbs mentioned above. Essentially, it is a TNF receptor Fc fusion protein that mainly competes with TNF-α to prevent it from binding to the TNF receptor on the cell surface. The TEMPO study conducted by Klareskog et al. showed that the combination of etanercept and methotrexate is superior to monotherapy in reducing RA disease activity, improving functional impairment, and delaying imaging progression [12]. These studies indicate that even if they belong to the same category of TNF-α inhibitors, the structural characteristics and combination therapy of different drugs can still affect their clinical efficacy.

3.2 Summary of The Mechanism of Action of TNF-α mAb

The core mechanism of action of TNF-α mAbs is to neutralize TNF-α and block its binding to TNFR1 and TNFR2, thereby inhibiting downstream inflammatory signaling pathways. After TNF-α is inhibited, the activation level of pathways such as NF-κ B and MAPK decreases, and the expression of pro-inflammatory cytokines, chemokines, and adhesion molecules decreases accordingly. The infiltration of inflammatory cells in synovial tissue is also inhibited. Therefore, TNF-α inhibitors can quickly improve clinical symptoms such as joint swelling, pain, and morning stiffness, and their role is to intervene upstream in the inflammatory cascade.

However, TNF-α is not the only inflammatory driver in RA. Some patients, even with treatment with TNF-α inhibitors, still cannot achieve low disease activity or remission. Lewis et al. found in their study based on the British College of Rheumatology Biologics Registry database that baseline disease activity, functional status, and concomitant medication may all affect the response to anti TNF therapy in patients [10]. This indicates that the pathological mechanism of RA has significant heterogeneity, and different patients may rely on different inflammatory pathways. Therefore, future treatment needs to pay more attention to precise typing and personalized medication.

4. Safety Characteristics and New Progress of TNF - α Monoclonal Antibody drugs

4.1 Safety and Adverse Reactions

Although TNF-α inhibitors have shown significant efficacy in the treatment of RA, its safety should not be ignored. Because TNF-α plays an important role in host anti infection immunity, long-term inhibition of TNF-α may weaken the body's ability to remove pathogens, thereby increasing the risk of infection. A recent national cohort study in Japan also confirmed that the use of TNF-α inhibitors would increase the risk of severe infection in patients with rheumatoid arthritis [13]. This result shows that when using TNF-α inhibitors in clinical practice, we should not only pay attention to the curative effect, but also evaluate the risk of infection.

Tuberculosis infection is one of the most worrying adverse reactions when using TNF - α inhibitors. Dixon et al. Showed that the risk of tuberculosis associated with different TNF - α inhibitors may be different. The risk of infliximab and adalimumab is relatively high, while the risk of etanercept is relatively low [14]. This finding has strong clinical significance, because it suggests that doctors should assess the patient's TB exposure history before drug selection, and conduct TB screening before treatment.

In addition to infection, immunogenicity is also an important factor affecting the long-term efficacy of TNF-α inhibitors. Some patients may produce drug-resistant antibodies during treatment, resulting in reduced blood drug concentration, weakened efficacy, and even infusion reactions. Fernandez CA's research shows that the combined use of traditional anti rheumatic drugs (DMARDs) such as methotrexate can reduce the formation of drug-resistant antibodies, so as to maintain the efficacy of anti TNF drugs and prolong the drug retention time [15]. This explains why in clinical practice, TNF - α inhibitors are usually used in combination with methotrexate rather than as a single therapy.

4.2 New TNF-α Inhibitor

In recent years, one of the important directions in the research of TNF-α inhibitors is the development of biosimilars. With the expiration of the original TNF-α inhibitor patents, biosimilars such as adalimumab, infliximab, and etanercept are gradually entering clinical practice. Biosimilars are not generic drugs in the ordinary sense, but drugs that are highly similar in structure, function, efficacy, and safety to original biological preparations. Rezk and Pieper pointed out that the promotion of anti TNF biosimilars can help reduce treatment costs and improve patient accessibility to biologics [16]. This is particularly important for RA patients who require long-term treatment, as economic factors often directly affect the sustainability of treatment. Clinical studies have gradually supported the similarity in efficacy and safety between some TNF-α biosimilars and the original drug. After analyzing multiple studies comparing biosimilars with original TNF inhibitors, Smolen et al. pointed out that the overall performance of related biosimilars in controlling RA imaging progression is similar to that of the original drug [17]. This result indicates that biosimilars not only have economic significance but may also expand the coverage of standardized treatment in real clinical settings.

5. Conclusion

This article summarizes the immune imbalance mechanism of RA, focuses on the central position of the TNF-α signaling pathway in the inflammatory network, and analyzes in detail the mechanism of action and clinical research progress of TNF-α mAb drugs. The pathogenesis of RA is not driven by a single factor, but a complex immune disorder process involving T cells, B cells and a variety of inflammatory factors. As an upstream regulator of the inflammatory cascade, tumor necrosis factor-α (TNF-α) continuously amplifies joint inflammation and leads to bone destruction by activating nuclear factor-κB (NF-κb) and mitogen activated protein kinase (MAPK). TNF-α inhibitors, such as adalimumab, infliximab and etanercept, can significantly improve the clinical symptoms of patients with rheumatoid arthritis, delay the imaging progress and improve the quality of life by neutralizing TNF-α or blocking its binding with receptors. However, it is worth noting that long-term use of TNF - α inhibitors will increase the risk of infection (especially tuberculosis), and the formation of drug-resistant antibodies caused by drug immunogenicity will also affect the durability of curative effect.

This review is mainly based on integrated analysis of existing literature, lacking meta-analysis of raw clinical data or real-world research evidence, and the stratified evaluation of different subtypes of RA patients is not deep enough. Future research should focus on exploring biomarkers for predicting treatment response and promoting personalized medication strategies. At the same time, people need to develop new TNF-α inhibitors or combination therapy regimens to reduce immunogenicity and infection risk. In addition, for patients resistant to anti TNF therapy, it is necessary to further elucidate the mechanisms of alternative inflammatory pathways to provide theoretical basis for the development of next-generation targeted drugs.

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