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The Role of TNF- α Inhibitors in The Management of Gout Arthritis and Its Comparison with Other Modalities

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Abstract

Background: Gout arthritis is caused by the deposition of monosodium urate crystals in the joints, which can cause significant pain, swelling, and recurring inflammation, particularly in the big toe. Inflammatory mediators are critical to the beginning and duration of the inflammatory response in gout arthritis. Gout is mediated by TNF-α, ILs, and the NLRP3 inflammasome, which promotes macrophages, monocytes, and neutrophils, leading to inflammatory reactions. TNF-α acts as a potent inflammatory mediator by stimulating the expression of other inflammatory cytokines, adhesion molecules, and matrix metalloproteinases (MMPs). TNF-α interacts with particular receptors and activates intracellular signaling pathways, leading to leukocyte recruitment, NLRP3 inflammasome activation, and the release of other inflammatory mediators. **Objective:** This article is a review article in which the researchers examine the current state of understanding regarding the role of TNF-α as a major inflammatory mediator in gout arthritis, deepen the understanding of TNF-α in gout inflammation, and explore its potential as a therapeutic target. **Method:** It involved systematically searching relevant databases, selecting studies based on inclusion criteria, and synthesizing findings to identify trends, gaps, and the current state of knowledge on the topic. **Result:** The results of this review article indicated that TNF-α plays a crucial role in joint inflammation by triggering the release of pro-inflammatory cytokines and stimulating neutrophil infiltration into the joints. **Conclusion:** Thus, Inhibiting TNF-α can reduce inflammation and improve symptoms in people with gout arthritis.

Keywords: Gout Arthritis, TNF-α, Inflammatory Mediator, Therapy

Review Article

INTRODUCTION

Gout arthritis is a form of arthritis characterised by severe episodes of pain, swelling, and recurrent inflammation in the joints, particularly affecting the big toe. (Dalbeth et al., 2016) This condition is caused by the deposition of monosodium urate crystals in the joints, which triggers an inflammatory response through various inflammatory mediators. (Sivera et al., 2022; Zha et al., 2022)

Inflammatory mediators play a crucial role in the initiation and prolongation of the inflammatory response in gout arthritis. Various mediators such as inflammatory cytokines, chemokines, and various signaling molecules play a role in coordinating the recruitment and activation of immune cells, such as neutrophils and macrophages, leading to tissue damage and inflammation. Specifically, tumor necrosis factor-alpha (TNF-α), certain interleukins (IL), and NOD-like receptor protein 3 (NLRP3) inflammasome mediate the development of gout and induce a series of amplification reactions in the inflammatory cascade through the participation of macrophages, monocytes, and neutrophils. (Zha et al., 2022)

TNF-α is an inflammatory cytokine produced by various cell types, including macrophages, monocytes, and synoviocytes. TNF-α acts as a potent inflammatory mediator, inducing the expression of other inflammatory cytokines, adhesion molecules, and matrix metalloproteinases (MMPs). Through its interaction with specific receptors, TNF-α triggers intracellular signaling pathways that promote leukocyte recruitment, activation of the NLRP3 inflammasome, and the release of additional inflammatory mediators. (Jang et al., 2021; McGeough et al., 2017; Yokose et al., 2017)

This review aims to examine the role of TNF-α as the main inflammatory mediator in gouty arthritis. By deepening the understanding of TNF-α in gouty inflammation, it is hoped that we can understand the contribution of TNF-α to the pathogenesis of gouty arthritis and its potential as a therapeutic target.

DISCUSSION

Development and Role of Inflammatory Mediators in the Pathogenesis of Gout Arthritis

Gouty arthritis is a complex inflammatory disease characterised by the deposition of monosodium urate (MSU) crystals within the joints and surrounding tissues. Gout occurs due to ongoing hyperuricemia (serum uric acid ≥360 µmol/L), which causes intra- and/or periarticular deposition of MSU crystals. (Abhishek et al., 2017) In susceptible individuals, oversaturated uric acid levels lead to the formation of MSU crystals, which trigger an immune response and initiate the pathogenesis of gouty arthritis. (Abhishek et al., 2017; Ragab et al., 2017)

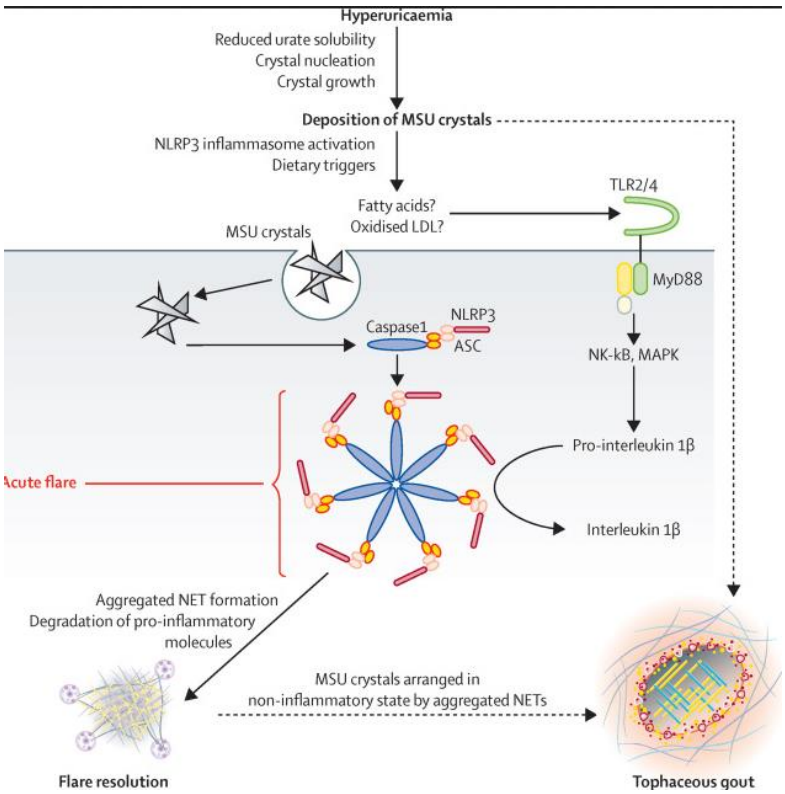

Figure 1. The progression from hyperuricemia to clinical gout arthritis. (Dalbeth et al., 2016)

After MSU crystals form, resident macrophages and other mononuclear cells will phagocytize them and induce inflammation by activating the NALP-3 inflammasome, which triggers the cleavage of pro-IL-1β and the secretion of IL-1β. This process is facilitated by spatial co-localization through microtubules with mitochondria, involving α-tubulin acetylation. Caspase 1, recruited by the activated inflammasome, processes pro-interleukin 1β into mature interleukin 1β. The inflammatory response then escalates due to the activation of neutrophils and mast cells, leading to the release of various pro-inflammatory cytokines, chemokines, and other factors such as reactive oxygen species, prostaglandin E2, and lysosomal enzymes. (Dalbeth et al., 2016) Since macrophage impairment in the NALP-3 inflammasome does not increase the inflammatory response to MSU crystals, NALP-3 inflammasome activation is essential to the inflammation caused by MSU crystals. (Abhishek et al., 2017; Kingsbury et al., 2011) Once activated, monocytes and macrophages release chemokines (CXCL-1, IL-8, and G-CSF), promoting neutrophil chemotaxis, survival, and proliferation. Other chemokines, such as CCL-2, recruit additional macrophages and monocytes, which will secrete TNF-α (promoting cellular activation, endothelial adhesion, and phagocytosis) and IL-1β (promoting endothelial adhesion, endogenous pyrogen), causing a strong inflammatory response that spreads from the initial site where neutrophils release lysozyme in an attempt to phagocytose MSU crystals. (Cronstein & Terkeltaub, 2006; Galozzi et al., 2021)

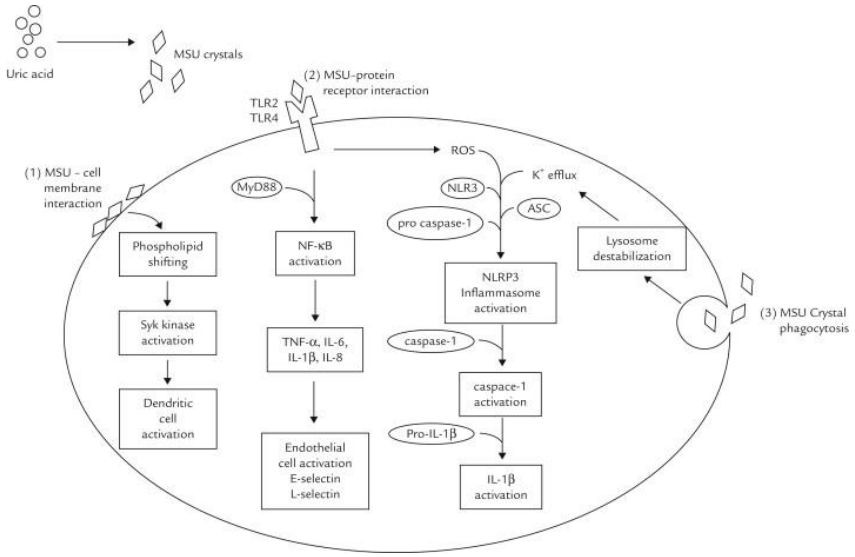

Figure 2. The signaling of inflammatory cytokines in MSU crystal-mediated inflammation (Dalbeth et al., 2014)

The interaction between TNF-α and IL-1β has been shown to significantly enhance various biological inflammatory functions, both in vitro and in vivo. Not only does it enhance the production of IL-1β, but TNF-α also increases the secretion of IL-1β and the activation of caspase-1, an essential component of the inflammasome complex responsible for the processing and release of IL-1β in macrophages and dendritic cells. Although the effects of TNF-α and IL-1β overlap to some extent, they may have slightly different roles in the inflammatory cascade. Decreasing TNF-α leads to a significant decrease in the levels of IL-1β and IL-18 in serum, indicating the importance of TNF-α in inflammation. (Aggarwal, 2003) Hence, TNF-α can be said to play a central role in gout arthritis inflammation through its pro-inflammatory action, synergistic effects with IL-1β, and its ability to regulate other important pro-inflammatory cytokine levels. (Aggarwal, 2003; McGeough et al., 2017; Yokose et al., 2017)

TNF-α: Receptor: Signaling Pathway and Inhibition Mechanisms

Tumor necrosis factor-alpha (TNF-α), also known as tumor necrosis factor superfamily member 2 (TNFSF2), is a pleiotropic cytokine capable of mediating inflammatory responses, regulating immune function by promoting activation and recruitment of immune cells, and triggering proliferation,

differentiation, apoptosis, and necroptosis of cells. (Holbrook et al., 2019) TNF-α is primarily produced by activated immune cells, and its increased circulation can be detected within minutes after pro-inflammatory stimulation; TNF-α can also be expressed by activated endothelial cells, fibroblasts, adipose tissue, cardiac myocytes, and neurons. TNF-α involves numerous mechanisms and depends on the regulation and relative expression of two receptors, as well as its release. (Aggarwal, 2003; Holbrook et al., 2019)

The pleiotropic actions of TNF-α are mediated by one of its two TNF receptors, TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2), which involve distinct downstream signaling pathways; hence, they exhibit both common and distinct biological functions. (Kalliolias & Ivashkiv, 2016) TNFR1 is generally expressed in all human cells and is more efficiently triggered by the hydrophilic form of TNF-α, whereas TNFR2 is predominantly expressed in immune cells, endothelial cells, and neurons and has a higher affinity for the membrane-bound form of TNF-α. Binding of TNF-α to TNFR1 largely promotes inflammation and tissue injury, whereas binding to TNFR2 is primarily involved in immune modulation and tissue regeneration. TNFR2 is also crucial for epithelial-mesenchymal transition and cell proliferation. (Holbrook et al., 2019; Imaizumi et al., 2022)

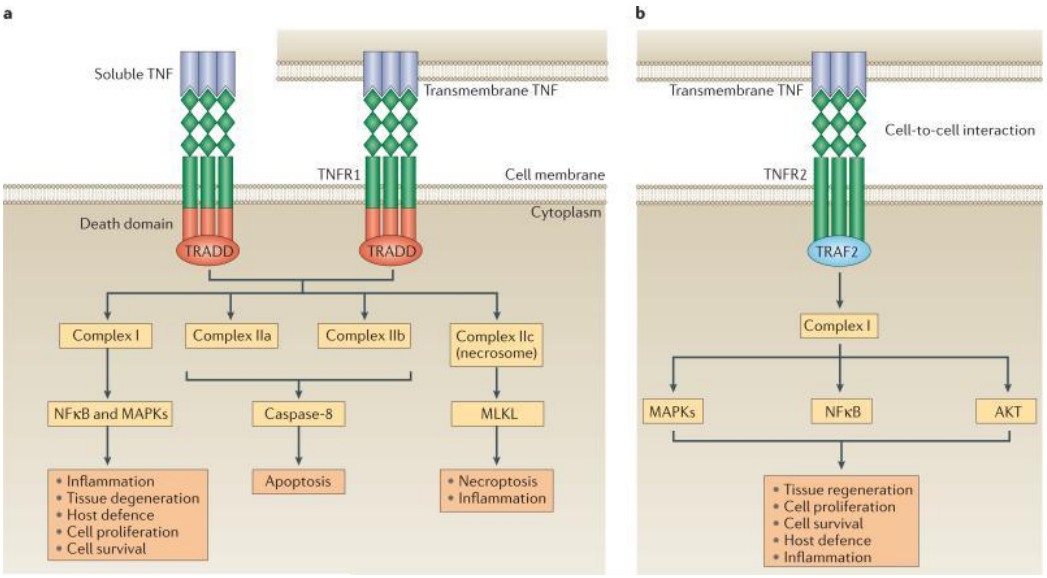

Figure 3. The signalling and biological activities of the TNF-α receptor (Kalliolias & Ivashkiv, 2016)

Activation of TNFR1 plays a role in many of the common inflammatory responses typically associated with TNF-α. The trimeric TNF-α binds to the extracellular domain of TNFR1, releasing the protein inhibitor, silencer of death domains (SODD), from the intracellular domain of TNFR1. The oligomerized intracellular domain of TNFR1 then binds to the adaptor protein TNF receptor-associated death domain (TRADD), which recruits additional adaptor proteins: receptor interacting protein-1 (RIP-1), serine/threonine kinase, and TNFR-associated factor 2 (TRAF2), an E3 ubiquitin ligase. This TRADD-RIP-1-TRAF2 complex is then internalised and dissociated from TNFR1. These adaptor proteins are involved in activating the main signalling pathway. Recruitment of MEKK-3 and transforming growth factor-β (TGFβ)-activated kinase (TAK1) by RIP-1 then activates the inhibitor κB kinase (IKK) complex. The IKK complex then phosphorylates (mainly by IKKβ) IκBα and other IκB proteins, leading to the ubiquitination and degradation of IκBα, causing the release of NFκB subunits that were previously bound to IκBα under unstimulated conditions. (Chen et al., 2018; Holbrook et al., 2019; You et al., 2021) The free NFκB subunits then translocate into the cell nucleus and initiate gene transcription. Thus, there are variations in signalling mediators depending on the cell type in the TNF-α-induced signalling pathway. TNF-α-induced NFκB activation in macrophages depends on G protein-coupled receptor kinases 2 and 5. G protein-coupled receptor kinases were initially discovered for their role in

desensitising G protein-coupled receptors. In recent studies, we found that GRK2 and GRK5 can directly interact with and phosphorylate IκBα as well as mediate TNF-α-induced NFκB activation in macrophages. GRK5 serves as a negative regulator of NFκB signaling in endothelial cells, and the role of GRK5 in this context is independent of kinase activity in endothelial cell lines. (Chen et al., 2018; You et al., 2021)

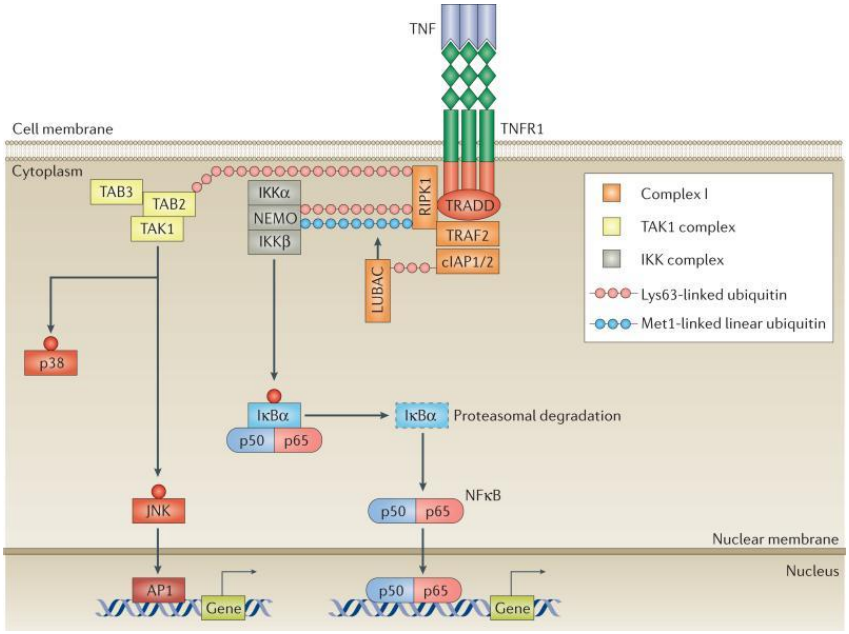

Figure 4. TNFR-1 signalling complex model (Kalliolias & Ivashkiv, 2016)

While the normal signaling pathway of TNF-α plays a critical role in regulating immune responses and inflammation, excessive or prolonged activation of this pathway can lead to various chronic inflammatory conditions. To mitigate such effects, TNF-α inhibitors have been developed, targeting specific points in the pathway to block or reduce the harmful activity of TNF-α. The mechanisms of action of TNF inhibitors involve the lysis of cells through two main pathways: complement-dependent cytotoxicity (CDC) via the classic complement pathway or antibody-dependent cellular cytotoxicity (ADCC) via Fc receptors. (Cessak et al., 2014) Early studies have shown that anti-TNF agents, including the monoclonal antibodies (mAbs) infliximab, adalimumab, certolizumab, and golimumab, as well as the soluble TNF-α receptor etanercept, neutralize the activity of soluble TNF-α by binding to the TNF-α dimer interface, forming a complex that prevents TNF-α from binding to its receptors. By doing so, they prevent its interaction with TNF-α receptors 1 (TNFR1) and 2 (TNFR2), thereby inhibiting the downstream inflammatory responses. (Evangelatos et al., 2022) These drugs also feature an Fc region—either naturally occurring, as in monoclonal antibodies, or genetically fused, as in etanercept—which binds to Fc receptors (FcR) on immune cells like monocytes, macrophages, NK cells, and platelets. This interaction can activate or inhibit immune functions depending on the specific type of Fc receptor involved. (Jang et al., 2021; Zia et al., 2020) These therapeutic strategies have shown significant success in treating chronic inflammatory conditions driven by excessive TNF-α activity. (Muth et al., 2023; H. Zhang et al., 2021) With this understanding, we can now explore the specific role of TNF-α in MSU crystal-induced inflammation and how it contributes to conditions like gout.

The Role of TNF- α In MSU Crystal-Induced Inflammation

The main pathological feature of gout is the accumulation of neutrophils in the joint fluid, which corresponds to endothelial activation by IL-1 and TNF-α, resulting in the expression of adhesion molecules for leukocytes. (Cronstein & Terkeltaub, 2006) Neutrophils accumulate in both the joint fluid and synovial membrane, where a small portion of these cells actively phagocytose MSU crystals and

release mediators. (Schett et al., 2015) These mediators include abundant cytosolic neutrophil proteins, S100A8/S100A9 (previously known as crystal-induced chemotactic factor [CCF]), which are low molecular weight mediator molecules such as prostaglandins and leukotrienes that are chemotactic and amplify the inflammatory response. (Cronstein & Terkeltaub, 2006; Wang et al., 2018)

The innate immune inflammatory response to the surface of MSU crystals, which likely releases surface-bound proteins, including apolipoprotein B bound to the crystal surface with anti-inflammatory properties, as a boundary of the expanding and shrinking MSU crystal deposits, is highly implicated in gout pathology. This process involves the formation of a terminal membrane attack complex (MAC) triggered by C5 cleavage on the crystal surface, as well as the ability of MSU crystals to activate resident cells in the joints and stimulate the production of IL-8 and related chemokine receptor ligands. (Cronstein & Terkeltaub, 2006) Formation of the inflammasome in response to MSU crystals triggers caspase-1 activation as well as maturation and secretion of IL-1β in phagocytes, and the formation of the NALP3 inflammasome protein complex induced by MSU crystals is suppressed by the microtubule inhibitor, colchicine. Other events associated with early innate immune response in gout inflammation include expression on infiltrating phagocytes of triggering receptor expressed on myeloid cells-1 (TREM-1). (Cronstein & Terkeltaub, 2006; Ragab et al., 2017)

The Role of TNF-α Inhibitors in the Management of Gout Arthritis and its Comparison with other Modalities

The management of gout arthritis involves immediate management of acute attacks and effective long-term uric acid management. Managing acute attacks requires rapid and effective control of the inflammatory response to MSU crystals, thereby reducing pain and swelling in the joints. (Coburn & Mikuls, 2016; Dalbeth et al., 2016) Current treatment guidelines recognise the efficacy of colchicine in the treatment of acute gout arthritis and in the prevention of gout attacks. The American College of Rheumatology, in its Gout Management Guidelines, recommends pharmacological treatment of acute gout within 24 hours of onset and recommends colchicine, NSAIDs, selective cyclooxygenase-2 inhibitors, and corticosteroids as first-line therapies to treat pain from acute attacks. (Dalbeth et al., 2014; Ragab et al., 2017)

Colchicine affects the underlying molecular pathology of acute gout arthritis inflammation in a multimodal manner. Colchicine binds to both α- and β-tubulin to form a tubulin-colchicine complex that prevents microtubule formation. The disruption of microtubules by colchicine is the primary mechanism by which colchicine intervenes in the molecular processes underlying gout inflammation. Additionally, colchicine also interferes with the activation of the NLRP3 inflammasome by MSU crystals, thus preventing the processing of pro-IL-1β and the release of IL-1β. (Dalbeth et al., 2014; Leung et al., 2015) Colchicine suppresses TNF-α-induced macrophage activation and reduces the number of TNF-α receptors on the surface of macrophages and endothelial cells, but not on the surface of neutrophils. These findings are attributed to microtubule destabilization influenced by colchicine. TNF-α-induced NF-κB activation is also inhibited by colchicine. Previous research evidence indicates that microtubules play a crucial role in regulating the signalling cascade involved in NF-κB activation. Microtubule disruption caused by colchicine inhibits signal transduction in the TNF-α-NF-κB pathway. (Dalbeth et al., 2014)

Considering the central role of TNF-α in the pathogenesis of gout, the use of TNF-α inhibitor therapy in the management of gout arthritis has become a topic of significant research and clinical interest. (Lis et al., 2014; Min et al., 2022) Treatment with TNFα antagonists for indications including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriatic arthritis (PsA), juvenile chronic arthritis (JCA), psoriasis, and ankylosing spondylitis (AS) has been widely employed.(Lin et al., 2008) Following impressive results from randomised clinical trials in the mid-1990s and since its distributor licencing in 1998, TNF-α inhibitors have proven effective for treating various inflammatory diseases. (Evangelatos et al., 2022) In recent years, TNF-α inhibitors have been utilised as a therapeutic strategy to control inflammation associated with gout arthritis. (Y. Zhang et al., 2020) TNF-α inhibition has been

shown to be effective in reducing symptoms and preventing acute attacks in patients with gout arthritis. Clinical studies and practical experience have provided strong evidence of the effectiveness of this therapy in reducing joint pain, swelling, and other inflammatory symptoms associated with gout arthritis. (Amaral et al., 2016; Y. Zhang et al., 2020)

Five TNF-α inhibitors were approved for use in 2008, with three TNF-α inhibitors: Etanercept, Infliximab, and Adalimumab becoming the best-selling types among all classes. (Lis et al., 2014) Initial studies have established that TNF-α inhibitors, namely the anti-TNF-α monoclonal antibodies (mAbs) Infliximab, Adalimumab, Certolizumab, and Golimumab, and the hydrophilic TNF-α receptor Etanercept, work by neutralizing the activity of hydrophilic TNF-α and preventing its binding to TNFα receptor 1 (TNFR1) and TNFR2. (Evangelatos et al., 2022)

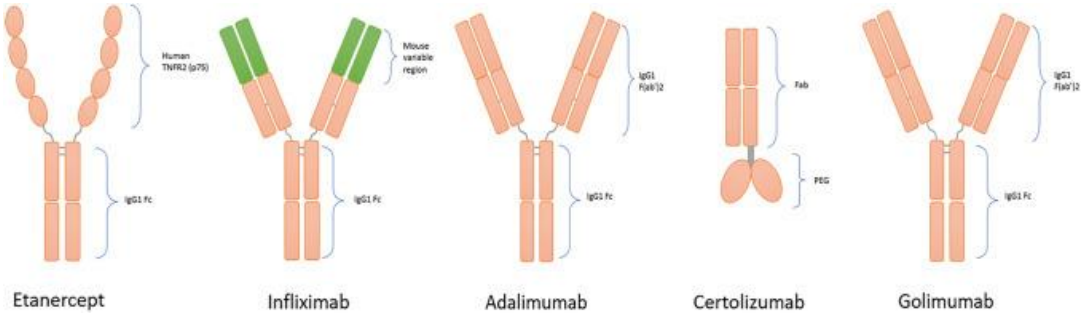

Figure 5. The molecular structure of approved TNF-α inhibitors(Evangelatos et al., 2022)

In general, TNF-α inhibitors act on the body's immune system as follows: (a) reducing the expression of pro-inflammatory cytokines, chemokines, acute-phase proteins, and adhesion molecules; (b) increasing the circulating number of regulatory T cells; and (c) reducing the migration of inflammatory cells from the blood to inflamed tissues. Etanercept also neutralizes lymphotoxin, while anti-TNF agents possess cell cytotoxic properties by binding directly to TNF-α transmembrane expressed on various cells. The binding of TNF-α inhibitors to TNF-α transmembrane affects intracellular signaling and, besides causing programmed cell death, can also lead to the suppression of cytokine production or cell growth inhibition. (Evangelatos et al., 2022; Jang et al., 2021) In addition to effects on immune cells, the mechanism of action of TNF-α inhibitors also includes reducing vascular permeability and angiogenesis, as well as halting the activity of epithelial, endothelial, and mesenchymal cells. Recent advances in basic research indicate that TNF-α inhibitor therapy works by disrupting TNF-α signalling in mesenchymal cells. For example, specific TNFR1 triggers on mesenchymal cells play a crucial role in the development of TNF-dependent acute and chronic arthritis in mouse models. Meanwhile, the presence of inhibitor of kinase B kinase 2 (IKK2) in joint mesenchymal cells contributes to cartilage destruction and bone erosion; without IKK2, the progression of synovitis continues, resulting from local immunogenic synovial fibroblast necroptosis. Deletion of IKK2 affects arthritis gene expression and anti-apoptosis, leading to hypersensitization of synovial fibroblasts to TNF/receptor-interacting serine/threonine kinase 1 (Ripk1)-mediated necroptosis through different mechanisms, depending on acute or chronic TNF-α signaling. Moreover, Ripk3 is not required for TNF-mediated arthritis but is necessary for synovitis in mice with specific IKK2 deletion in mesenchymal cells, clearly indicating that the TNFR1-IKK2-Ripk-mixed-lineage kinase domain-like (MLKL) signalling pathway regulates arthritogenic responses and death in synovial fibroblasts and that combined inhibition of nuclear factor kappa beta (NF-κB) and MLKL/RIPKs may offer therapeutic potential. (Evangelatos et al., 2022; Monaco et al., 2015)

Developments and Future Research in Anti- TNF-α

Although TNF-α inhibition has shown significant efficacy in the treatment of gout arthritis, there are still challenges and limitations that need to be addressed. Firstly, not all patients with gout arthritis will respond well to treatment. Therefore, research to identify predictive factors that can help select

patient demographics with a high probability of responding well to treatment is needed. Secondly, therapies targeting TNF-α tend to be costly and may not be widely available to all patients with gout arthritis. Accessibility to these therapies may be a constraint in some countries or healthcare systems. Therefore, efforts are needed to improve accessibility to these therapies and find more affordable solutions.

CONCLUSION

In gout arthritis, TNF-α plays a central role as an inflammatory mediator, causing joint inflammation. Activation of TNF-α results in the release of pro-inflammatory cytokines and stimulates neutrophil infiltration into the joints, leading to pain and swelling in gout arthritis. The introduction of TNF-α inhibitors as therapy in gout arthritis has shifted the treatment paradigm and improved disease management. Targeting TNF-α has been proven effective in controlling inflammation and alleviating symptoms in patients with gout arthritis. However, the challenges and limitations associated with this therapy need to be considered. Further research is required to optimise the use of this therapy and identify new therapeutic approaches that are more affordable and effective in managing gout arthritis.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

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