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Exploring disease therapeutic strategies by modulating the TNF-α/NF-KB signalling pathway

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Abstract. In recent years, the number of patients with rheumatic diseases such as ankylosing spondylitis has been increasing, with over 3 million young people suffering from the disease. One main causal factor for these diseases is tumour necrosis factor-a (TNF-a), a pro-inflammatory cytokine that triggers mutations and apoptosis of various cell types by activating multiple signalling pathways. NF-KB is an essential intracellular nuclear transcription factor that participates in the inflammatory and immune responses of the organism and regulates apoptosis and stress responses. Excessive activation of NF-KB has been linked to inflammatory changes in various human diseases, such as rheumatoid arthritis, cardiovascular diseases, etc. Therefore, inhibition of the NF-KB signalling pathway by drugs may become a therapeutic approach. Among multiple signalling pathways that induce inflammation, the TNF-α/NF-KB signalling pathway is considered the most important. This review will discuss the relevant diseases for which modulation of the TNF-α/NF-KB signalling pathway is the main therapeutic strategy. These strategies include targeted inhibition by blocking the TNF-a/NF-KB signalling pathway, modulation of inflammatory factor transmission at the nanoscale by ribonucleotides, and Oncolytic virus therapy. Some of these strategies are effective and have been applied to treat multiple diseases; others are still in the exploratory phase, but the potential of these exploratory therapies is enormous and promises to overcome the limitations of traditional therapeutic strategies.

Keywords: TNF-a, Pro-inflammatory cytokine, NF-KB, Signalling pathway.

1. Introduction

In recent years, ankylosing spondylitis has become a common rheumatic disease, and this disease has been mostly found in young men, and the number of ankylosing spondylitis patients has exceeded 5 million in China, and the trend is gradually increasing [1].

The main element contributing to the appearance of these diseases is tumour necrosis factor (TNF)-a, which is a potent pro-inflammatory cytokine in inflammatory diseases. In addition, TNF-a has a critical function in developing systemic inflammatory diseases such as leukodystrophy [2]. During inflammatory, TNF-a is an essential pro-inflammatory cytokine with multiple effects on different cells through the activation of intracellular nuclear factor-kappa B (NF-KB), mitogen-activated protein kinase, and caspases [3]. TNF-a is a ligand component of the TNF superfamily, which recognizes explicitly 29 receptors, constituting a ligand-receptor system of interaction [4]. Those TNF receptors (TNFRs) are

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mainly transmembrane proteins involved in several physiological processes such as host defense, inflammation, apoptosis, autoimmunity, as well as immunity, ectodermal and neurological development, and organogenesis [5].

TNF-a is an essential pathway in the TNFRs. TNF-a and the inflammatory factor Interleukin-1 (IL-1) are major extracellular stimulators that induce tumour formation and inflammation formation, and these extracellular stimulatory signals activate the NF-KB signalling pathway [6].

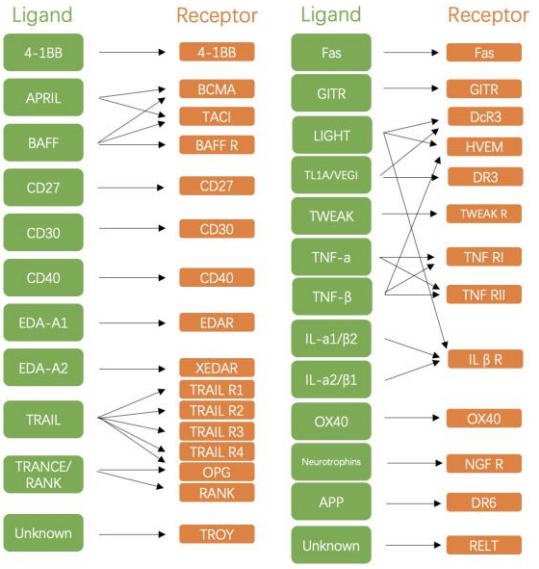

Figure 1. TNF Superfamily Pathways: ligand-receptor interactions and their associated functions in humans. Some of the ligands have multiple receptors at the same time [7].

The NF-KB signalling pathway consists of the receptor and receptor proximal signalling interface proteins, the IκB (inhibitory NF-KB) kinase complex (IKK complex), IκB proteins, and the NF-KB dimer [8]. These proteins are involved in controlling DNA transcription, cytokine production, and cell survival [9].

Among them, the IKK complex consists of IKKa, IKKβ, a major kinase, and IKKγ.

During the process of the canonical NF-KB signalling pathway, TNF-a acts as an extracellular stimulatory signal, TNF receptor-associated factors (TRAFs), which are upstream of the IKK complex, receive the signal and phosphorylate the kinase IKKβ, resulting in the activation of NF-KB by pro-inflammatory factors [10]. The primary role of IκB proteins is to cover up the nuclear localisation signals of NF-KB, preventing it from entering the nucleus and binding to DNA so that NF-KB only exists in the cytoplasm in an inactivated state [11]. Once activated by the kinase IKKβ, the IκB protein is degraded and releases NF-KB dimers (p50, RelA) that are translocated to the nucleus.

NF-KB dimers act in the last step of this signaling pathway and contribute to initiating the transcription of target genes. These NF-KB dimers typically either bind to DNA or IκB [12]. While binding to DNA, NF-KB forms a heterodimer with either p65 or p50. While binding to IκB, NF-KB interacts with IκB through its C-terminal specific anchor protein repeat sequence (containing the amacrine repeat domain, ARD), and IκB further covers the NLS, which stops the movement of NF-KB to the nucleus [12].

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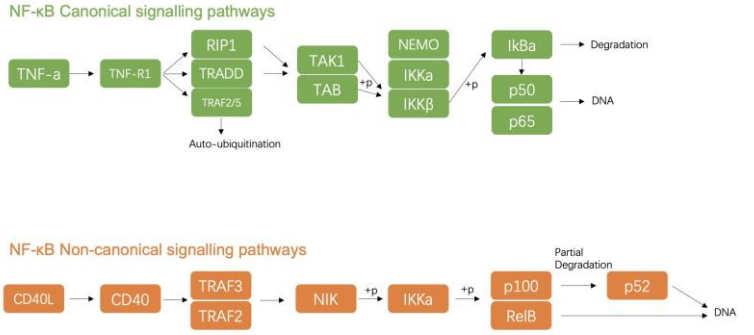

Figure 2. NF-KB signalling pathways. A: Figure 2A shows the canonical pathway; B: Figure 2B shows the non-canonical pathway. The KEGG pathway database is used for figure-making [13]

In addition, there are several non-canonical signalling pathways for NF-KB (Figure 2B). When specific TNF ligand family members (TRAF2, TRAF3, etc.) bind to corresponding receptors (CD40, etc.) to initiate the signalling, NF-KB induced kinase (NIK) is activated and then phosphorylates the protein kinase IKKa. IKKa facilitates the phosphorylation of p100 and RelB, but the p100 has to be degraded to p52, then both p52 and RelB can be translocated to the nucleus and further Induce downstream gene expression [14].

In this review, we will discuss relevant diseases with modulation of the TNF-α/NF-KB signalling pathway as the main strategy of treatment. These strategies include targeted inhibition by blocking the TNF-a/NF-KB signaling pathway, modulation of inflammatory factor conduction at the nano-level through tiny ribonucleotides, and oncolytic virus therapy.

2. Blocking pathway for therapy

Frontotemporal dementia (FTD) is a dementia syndrome that involves slow-onset personality changes and language deficits in elder patients and represents the most frequent form of dementia [15]. A major factor causing FTD is the Haploinsufficiency of the procyanidin (PGRN, GRN) gene [16,17]. Pathologically, patients with GRN deficiency exhibit increased microglia activation and astrocyte proliferation. Microglia are involved in a range of neurodegenerative diseases, microglia activation and neuroinflammation are key features of neuropathology. Under healthy conditions, microglia use their tiny branching processes to observe their surroundings, looking for any changes in homeostasis [18]. Upon injury, microglia are transformed into an activated state through morphological changes and discharge of pro-inflammatory agents, which cause further inflammatory responses [19]. In microglia, deficient PGRN will secrete large amounts of pro-inflammatory factor TNF-α, and TNF-α will induce inflammation [20,21]. Data from Krabbe et al. has shown that TNF-α stimulation caused remarkably more NF-KB activation in GRN-deficient cells than in GRN non-deficient cells, which indicated that PGRN deficiency enhanced TNFα-induced NF-KB signaling [22]. They also found that deleting Ikbkb specifically inactivated NF-KB in microglia cells by using an inhibitor of the Ikbkb gene encoding Ikkβ, and this strategy did not affect the normal expression of PGRN [22].

Similarly, by inactivating NF-KB, the damage to the blood-brain barrier (BBB) function caused by methamphetamine can also be treated. Methamphetamine (METH) is one of the newer drugs, and its abuse represents a serious public health problem, involving over 35 million users worldwide suffering from the side effects including arrhythmia, dyspnoea, etc. [23]. The METH induced neurotoxicity damages the blood-brain barrier [24]. Specifically, METH induces a significant neuroinflammatory response, often characterised by glial cell proliferation and elevated cytokine levels. In Vanessa et al. study, at levels that are associated with human abuse, METH leads to the release of TNF-α from brain endothelial cells and astrocytes, followed by the activation of the NF-KB pathway and the translocation

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of p65 to the nucleus, which stimulates the synthesis of subsequent cytokines [25]. Therefore, blocking the inflammatory factor pathway could be an effective approach.

In addition, most osteoarthritis (OA) use similar approaches targeting inhibition of TNF-α or downstream NF-KB signaling pathways. The temporomandibular joint (TMJ) is a synovial joint that controls important daily functions such as speaking, chewing, and breathing in humans [26]. And temporomandibular joint osteoarthritis (TMJOA) is one of the most frequent diseases [27]. In TMJ, the SZ harbors fibro chondral stem cells (FCSCs) [28,29]. During TMJOA, TNF-α, a catabolic factor of cartilage, is released [30,31]. TNF-α modulates FCSC-specific changes in TMJOA through activation of NF-KB signaling [32]. One of the universal methods is to use NF-KB monoclonal antibody to treat TMJOA, blockade of NF-KB largely maintained the normal stem cell capacity of FCSC [33]. This finding suggests that targeted inhibition of inflammatory factor pathways can block pro-inflammatory signalling in FCSCs and protect cell population and function, which are important cellular resources for providing chondrogenic progenitor cells to repair cartilage breaks and alleviate clinical symptoms.

This type of treatment can also be applied to treat Alzheimer's disease (AD). The onset of AD is very insidious, and it usually presents with a variety of clinical symptoms, such as memory impairment, executive dysfunction, and behavioral changes without people realizing it. As a neurodegenerative disease, Alzheimer's disease occurs mainly due to neuroinflammation [34]. The common medicine for AD is acetylcholinesterase inhibitors (ACHEIs), which improve cognitive function in patients. The Nafea et al. showed that Leflunomide and the acetylcholinesterase inhibitor rivastigmine, which execute good anti-inflammatory and immunomodulatory effects, can have therapeutic and neuroprotective effects in AlCl3-induced AD rats when the two drugs are used in combination, and it can effectively inhibit the signaling of NF-KB, TNF-α, and IL-1β [35].

In summary, Blocking the inflammatory factor pathways remains the most direct and effective way to inhibit the inflammatory response, and this therapeutic strategy has shown significant improvement in several neurological diseases, osteoarthritis, etc. [22]. Therefore, drugs targeting inhibition of the inflammatory factor pathways remain the focus of today's therapeutic inflammatory strategies.

3. MicroRNA regulates the pathway

MicroRNAs (miRNAs) are small, highly conserved, non-coding RNAs that regulate gene expression and functions mainly by inhibiting the translation of target gene proteins or degrading target mRNAs [36]. miRNAs can participate in a wide range of cellular life processes and are strongly related to a multitude of diseases, such as tumors and cardiovascular diseases [37].

miRNA has been proposed for use in treating Bone defects. Bone defects are Bone defects caused by trauma or surgery that will not heal without interventional treatment of the bone tissue. [38,39]. Nowadays, most bone healing is treated with surgery and medication, and the drugs selected are mostly bone resorption inhibitors or calcium supplements. Melatonin is a polybiotic effects molecule with anti-inflammatory properties [40,41]. When Melatonin was applied, the inflammatory pathway was suppressed, whereas miR-335-5p expression was significantly enhanced [42]. miR-335-5p negatively affects inflammatory signaling, whereas miR-335-5p inhibitor ameliorated the effect of melatonin on inflammatory signaling. This promotion of osteogenesis was associated with increased miRNA and inhibition of TNFα/NF-KB in bone marrow stromal stem cells (BMSCs) [42].

miRNAs could also be used to regulate Abdominal aortic aneurysms (AAA). AAA is a highly fatal disorder that manifests itself as permanent dilatation of the abdominal aorta, which can ultimately cause the death of the patient [43,44]. The NF-KB p65 signaling pathway has a critical function in the regulation of inflammation, and its abnormal activation in the aorta promotes inflammatory factor expression [45]. NF-KB inhibitors have been reported to significantly inhibit AAA formation [46].

In these years of research on the origin and development of AAA, it has been found that miRNAs are implicated in the modulation of extracellular matrix degradation and smooth muscle cell apoptosis [47]. Ma et al. found that miR-195 could remarkably upregulate the expression of inflammatory factor proteins in angiotensin II vascular smooth muscle cells. They also found that miR-195 had pro-inflammatory effects on inflammatory factor protein expression and that TNF-α promoted the elevation

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of IL-1 and IL-6 levels [48]. Additionally, miR-195 can regulate hepatocellular carcinoma cancer cells through this pathway [49].

Similar to AAA, miRNAs can regulate intervertebral disc degeneration (IVDD). Intervertebral disc degeneration is closely associated with degenerative diseases of the spine [50,51]. IVDD is recognised by a reduction in the number and function of nucleus pulposus (NP) cells, leading to insufficient production of extracellular matrix (ECM) in the nucleus pulposus [52]. Pro-inflammatory cytokines inhibit ECM production in NP cells and increase degradative enzyme expression [53]. This pathogenesis is similar to the abnormal activation of the aorta in AAA, and a common therapeutic strategy is to use the Wnt signalling pathway associated with ECM metabolism that regulates inflammation in the NP [54]. Li et al. found that Wnt5a regulates TNF-a/NF-KB-induced matrix degradation through a negative feedback loop in IVDD [54]. However, the intervention of microRNAs may also have an ameliorative effect in two diseases with such similar pathological mechanisms, thus, microRNAs also provide new ideas for the treatment of IVDD [54].

In recent years, microRNAs-based nanomedicine therapies have been increasingly explored, which could overcome the drawbacks of existing therapies, such as reducing drug resistance and apoptosis due to drug therapy while trying to maximize drug efficacy [55]. Thus, modulation of the inflammation by microRNAs is a potentially good therapeutic strategy in the near future.

4. Oncolytic virus therapy

Oncolytic virus (OV) is a virus that infects and neutralises malignant cells through in vivo tumour lysing activity. It is a new and emerging therapeutic form that is widely regarded as a potential treatment option in patients suffering from malignant tumours [56]. Talimogene laherparepvec (T-Vec) is the first oncolytic virus to be used in the treatment of patients with melanoma and was validated by the US Food and Drug Administration (FDA) in 2015 [57].

In a recent study investigating the in vivo and in vitro lysogenic effect of NDV LaSota strain on spontaneous canine mammary carcinoma cell line (CMT-U27), Wang et al. found that NDV dramatically enhanced the expression level of TNFα and phosphorylation of p65 and activated the inflammatory factor pathway in CMT-U27 cells, after examining the genes and proteins related to the pathway [58]. Newcastle disease virus (NDV) is a single-stranded negative-stranded RNA (ssRNA) virus, and compared to other viruses, NDV is suitable for being an oncolytic virus because of its potent tumour lysis, strong immunogenicity, and tumour selectivity [59]. Once NDV is contracted, cancer cells activate apoptotic signalling pathways, leading to apoptosis [60,61].

Among other studies on NDV, it has been shown that NDV-induced apoptosis in human renal cancer cells is related to NF-KB activation [62]. Tumour lysis therapy is undoubtedly a different therapeutic approach, which no longer blocks the TNF-α/NF-KB signaling pathway or uses related inhibitors but activates the apoptotic signalling pathway to cause cancer cell death.

5. Conclusion

Nowadays, there is still great potential for using the modulation of the TNF-α/NF-KB signalling pathway to treat diseases.

The preferred option for the regulation of the Inflammatory factors remains to use targeted inhibitors of TNF-α/NF-KB to block the signalling. In addition, nanotherapeutic strategies with microRNAs as substrates have advantages over conventional therapeutic strategies. The pathological action of oncolytic viruses employs a completely opposite treatment approach, inducing apoptosis in cancer cells by stimulating the transmission of Inflammatory factors.

Among the therapeutic strategies for inflammatory diseases, targeted inhibitors remain the most effective and most researched drug type. Dimethyl fumarate (DMF) is a NF-KB signaling pathway inhibitor drug that was approved in the US and Europe in 2013 which is used in the treatment of multiple sclerosis and psoriasis [63]. In addition, there is also treatment for psoriatic arthritis and medial spondylarthritis with the latest inhibitor anti-inflammatory drug Bimzelx, which selectively and directly

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inhibits both IL-17A and IL-17F inflammatory factors and is already in the review phase in the European Union [64].

Meanwhile, with the fast growth of biopharmaceuticals and the emergence of COVID-19, gene therapy has begun to pay more and more attention, and since genes require specific carriers, miRNA-based nanocarriers have become one of the main research objects [65]. The advantages of nanotherapeutics can make up for the shortcomings of conventional inhibitors as it can enhance drug targeting and reduce enzymatic degradation. In a recent study, miR-34a mimics, a miRNA mimic, were shown to treat diseases characterized by miRNA downregulation [66]. Nanotherapeutics have shown great potential as an emerging therapeutic strategy.

Oncolytic viral therapy offers a unique approach to modulate cancer viruses and offers additional advantages over conservative cancer therapies: In certain situations when the targeted killing of the cancer cells is performed, these tumours may release associated antigens and trigger novel anti-tumour innate and adaptive immune responses [67]. Besides the approved T-Vec oncolytic virus, Myxoma virus (MYXV) is also a possible oncolytic virus, and there are teams recently investigating how MYXV could be developed as a therapeutic oncolytic virus for the treatment of human cancers [68].

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