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Post-transcriptional regulation of tumour necrosis factor alpha biosynthesis: Relevance to the pathophysiology of rheumatoid arthritis

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Abstract

Introduction

Expressed in response to injury or infection, tumour necrosis factor-alpha (TNF-α) is a highly potent mediator of inflammation. Controlled expression of TNF-α is crucial, since overexpression can lead to autoimmune disease and tissue damage. TNF-α expression is regulated at different levels, including transcription, mRNA turnover and translation. Many reviews have focused on the signalling pathways that mediate cellular responses following TNF-α receptor engagement. In this article, we focus on an aspect that shows promise for pharmaceutical intervention, namely intracellular mechanisms regulating production of TNF-α in immune cells, especially post-transcriptional checkpoints. We discuss the roles of adenosine-uridine-rich-element-binding proteins, micro-RNA and MAP kinase in the post-transcriptional regulation of TNF-α mRNA activity and their relevance to the physiopathology of rheumatoid arthritis.

Conclusion

A better understanding of the intracellular proteins and signalling pathways that regulate TNF-α biosynthesis is crucial to the development of novel anti-TNF-based therapies for rheumatoid arthritis patients.

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Introduction

Tumour necrosis factor-alpha (TNF-α) is a pleiotropic inflammatory cytokine produced mainly by activated macrophages, neutrophils, T lymphocytes and natural killer cells, and also by various other cells such as fibroblasts, smooth muscle cells and tumour cells. In addition to its known anti-tumour activity, TNF-α is now recognized as a key regulator of inflammatory responses, playing a variety of roles in the immune system including stimulation of inflammation, cytotoxicity, regulation of cell proliferation and adhesion and induction of cachexia. Systemic exposure to TNF-α can reproduce most of the symptoms observed in septicaemia by rapidly causing shock, tissue injury, capillary leakage, pulmonary oedema and multiple organ failure[1,2]. On the other hand, the increased incidence of infection in patients receiving anti-TNF treatment has highlighted the importance of TNF-α in combating infectious illness[3]. TNF-α interacts with two different receptors, designated TNFR1 and TNFR2[4], which are differentially expressed on cells and tissues and initiate both independent and overlapping signal transduction pathways, leading to multiple cellular responses.

Rheumatoid arthritis is a chronic inflammatory synovitis, characterized by marked hyperplasia of the synovial lining cells and eventual degradation of cartilage and the subchondral bone and by extensive infiltration of granulocytes, macrophages, lymphocytes and fibroblasts in joints, where numerous inflammatory mediators, including interleukins, chemokines, growth factors, proteolytic enzymes and eicosanoids, contribute to an ongoing process of inflammation[5]. In rheumatoid arthritis, neutrophils can play important roles in the pathogenesis of synovial inflammation. On a per cell basis, neutrophils produce relatively modest amounts of TNF-α, yet their sheer numbers at inflammatory sites make them an important source of this inflammatory mediator. Neutrophils may constitute more than 90% of the cellular exudate in the synovial fluid and are present in inflamed synovial tissue at the pannus–cartilage interface[6].

TNF-α is centrally involved in several inflammatory conditions, particularly in ankylosing spondylitis, inflammatory bowel disease, psoriasis and rheumatoid arthritis[7,8]. Studies in animal models have confirmed a pivotal role for TNF-α in the process of synovitis and joint destruction. Treating experimental models of arthritis with exogenous TNF-α induces or exacerbates synovitis. Furthermore, mice transgenic for TNF-α and mice with dysregulated TNF-α production both develop arthritis[9,10]. Treatment of murine arthritis with antibodies against TNF-α or with soluble TNF receptor ameliorates the disease[11,12]. In humans, clinical studies have demonstrated the unequivocal efficacy of anti-TNF therapy (using TNF-α-neutralizing antibody) in reducing the progression and symptoms of rheumatoid arthritis[13]. However, the US FDA has issued warnings in recent years against TNF blockers such as ENBREL®, since these drugs increase the risk of certain kinds of tumours in young individuals. Interventions

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involving control of TNF-α, therefore, need to be fine-tuned and different approaches need to be considered, for example, modulation of its production. The molecular mechanisms regulating TNF-α biosynthesis are only partly understood. Recent studies show the importance of post-transcriptional processes in controlling levels of TNF-α. We provide here an overview of this aspect.

Discussion

The authors have referenced some of their own studies in this review. The protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed.

Molecular Mechanisms Regulating the Biosynthesis of TNF-α

TNF-α is synthesized as a transmembrane protein with a molecular mass of 26 kDa. The propeptide is secreted as a soluble protein of 17 kDa upon cleavage by TNF-α-converting enzyme. However, regulation of TNF-α biosynthesis has been observed mainly at the levels of transcription, mRNA export, post-transcription and translation (Figure 1). Induction of TNF-α gene transcription is cell-type specific and stimulus specific, involving the recruitment of distinct sets of transcription factors to the promoter region, including NF-κB, Sp1, NF-AT, ATF-2, c-jun and CREB, among others[14]. Post-transcriptional regulation may influence the level of translation of mRNA and is mediated in part by specific and conserved sequences within the mRNA.

ARE of TNF-mRNA

AREs of the TNF-α mRNA molecule are critical for post-transcriptional regulation. They can control the
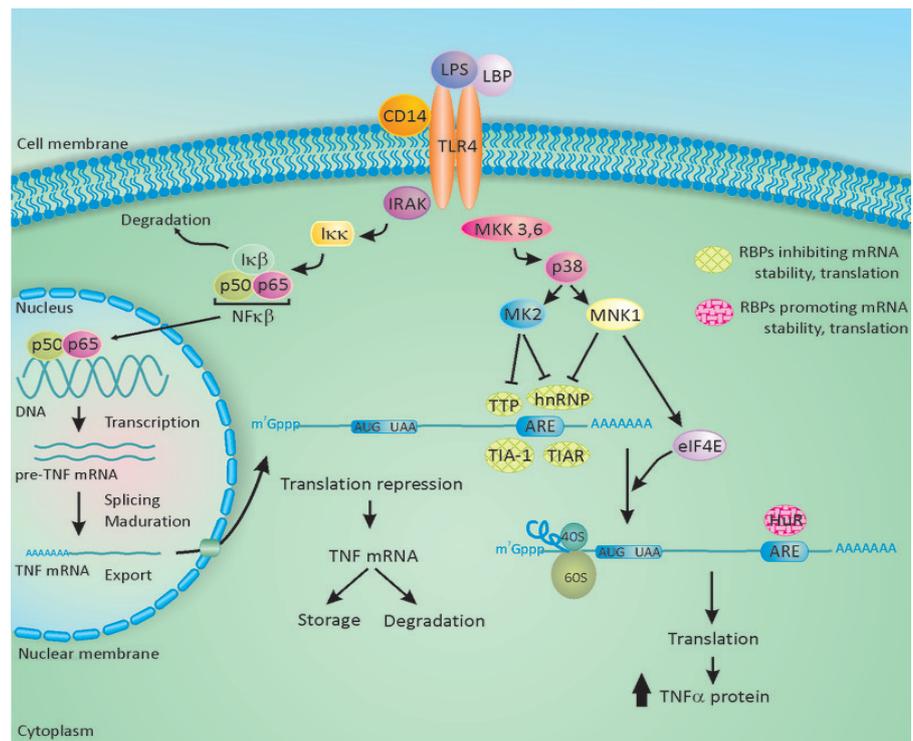

Figure 1: Schematic depiction of the regulation of TNF-α production: role of p38 MAP kinase and mRNA-binding protein in translational regulation.

LPS binds to serum protein LBP and is transferred to CD14 at the cell surface. LPS then interacts with toll-like signalling receptor 4 (TLR4) and activates two main pathways in the cells. One pathway leads to the activation of NF-κB (through IRAK and IKK), while in the other IκBα phosphorylation and degradation allow NF-κB to translocate into the nucleus and initiate TNF-α gene transcription. The mRNA primary transcripts (pre-TNF mRNA) are modified via editing of the sequence and/or modification of bases. Following processing, RNA is transported from the nucleus to the cytoplasm. Meanwhile, p38 MAP kinase is activated by LPS though MAPK kinases 3 and 6. Activated MAP kinase then phosphorylates RNA-binding proteins Mnk1 or MK-2, which stabilize TNF-α mRNA and regulate its translation by binding to ARE in the 3′-untranslated region, which otherwise make the mRNA unstable (i.e. rapidly degraded). TTP, TIA-1/TIAR and hnRNP-A1 are negative regulators, while HuR is a positive regulator of TNF-α production. For example, in inactive cells, hnRNP-A1 is bound to TNF-α mRNA, suppressing translation. Activation of the p38 MAP kinase pathways leads to phosphorylation of hnRNP-A1, releasing TNF-α mRNA from translational suppression. In addition, p38 MAP kinase regulates mRNA stability through activation of MK-2, which subsequently phosphorylates and inactivates TTP. Once inactivated, phosphorylated TTP dissociates from the ARE region of cytokine transcripts, thereby enhancing mRNA stability and translation and causing an increase in cytokine secretion, which can promote chronic inflammation and inflammatory disease progression if not properly regulated.

transport of the mRNA from the nucleus to the cytoplasm[15], destabilize the encoded message[16] and inhibit its translation[17]. AREs influence the stability or translation of a given mRNA, usually through binding of ARE-specific proteins and miRNA. Studying their role in resting

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macrophage TNF-α mRNA, Han et al. found that these elements imposed a strong translational blockade[17]. However, lipopolysaccharide (LPS) stimulation induced a significant rise in translational efficiency, leading to a strong induction of TNF-α production. In addition, transgenic mice that express TNF-α mRNA lacking ARE exhibit elevated levels of circulating TNF-α and develop chronic inflammatory arthritis and Crohn-like inflammatory bowel disease[16]. TNF-α ARE-mediated translational repression was observed subsequently in a variety of cell types, indicating that this mechanism was not specific to macrophages[18]. It was concluded that TNF-α ARE can act both as RNA instability determinants and as a translational modulator.

ARE-Binding Proteins
Several RNA-binding proteins that interact with ARE have been characterized *in vitro* and *in vivo*[19,20]. These proteins regulate RNA stability, transport and translation. Studies have shown that TNF-α mRNA translation could be regulated by a complex ensemble of RNA-binding proteins that are recruited to the 3′-untranslated region, such as heterogeneous nuclear ribonucleoprotein (hnRNP-A1), Hu antigen R (HuR, ELAVL1), T-cell intracellular Ag (TIA-1), TIA-1-related protein (TIAR) and tristetraprolin (TTP). Basal translation of TNF-α mRNA can be silenced by hnRNP-A1 binding to ARE, whereas TIA-1 and TTP prevent the pathological overexpression of TNF-α by acting downstream from toll-like receptor signalling. TIA-1 inhibits the translation of TNF-α transcripts, while TTP promotes the degradation of TNF-α transcripts[21–23]. HuR is a member of the embryonic lethal, abnormal vision-associated, *Drosophila*-like ELAV family of RNA-binding proteins. HuR is unique in stabilizing RNA transcripts involved in inflammation, such as those of cyclooxygenase-2 and TNF-α[24,25].

Although HuR is predominantly nuclear, it shuttles between the nucleus and the cytoplasm through a specialized domain, the HuR-shuttling domain. In addition to a proposed role for HuR in mRNA transport, its translocation to the cytoplasm has been linked to its mRNA-stabilizing function and its ability to modulate target mRNA translation. With respect to inflammation, studies on macrophage cell lines suggested that innate sensitizers increase binding of HuR to cytokine mRNA in the cytoplasm, thereby stabilizing these transcripts[26].

Although localized in the nucleus at steady state, hnRNP-A1 shuttles continuously between the nucleus and the cytoplasm, a property common to a subset of hnRNP[27]. It is also involved in post-splicing activities such as mRNA export[28] and cap-dependent and internal ribosome entry site-mediated translation[29]. In addition, a role for hnRNP-A1 in regulating mRNA stability has been suggested, based on data that support its ability to bind to ARE-rich sequences. Basal translation of TNF-α mRNA can be silenced by hnRNP-A1 binding to the ARE, while hnRNP-A1 phosphorylation by Mnk, a kinase downstream of p38-mitogen-activated protein kinase (p38-MAPK), decreases its affinity for ARE, thus reactivating TNF-α translation[21].

The TTP family of Cys-Cys-Cys-His tandem zinc-finger proteins is composed of three known members in mammals. TTP is known to bind to the so-called class II AU-rich elements within both TNF-α and COX-2 mRNA. In the case of TNF-α, this binding destabilizes the mRNA and results in decreased synthesis of the protein. Recent evidence suggests that TTP affects this accelerated mRNA degradation by first promoting removal of the polyadenylated tail (deadenylation). TTP-deficient mice develop a severe inflammatory syndrome with erosive arthritis, autoimmunity and myeloid hyperplasia. In patients with

rheumatoid arthritis, insufficient TTP production may be a contributing factor to increased disease severity[30]. Post-translational modification also contributes significantly in regulating the activities of TTP family proteins. These molecules are phosphorylated at several distinct sites in response to multiple signalling pathways[31]. The most extensively studied kinases in this context are the p38-MAPK and its downstream target MAP kinase-activated protein kinase-2 (MK-2), both of which appear to play a pivotal role in the regulation of ARE-mediated mRNA decay.

TIAR and its closely related homologue TIA-1 are members of the RNA-recognition motif family of RNA-binding proteins. Both have three recognition motif domains near the N-terminus, conferring high affinity for uridine-rich motifs[32]. TIA-1 and TIAR shuttle continuously between the nucleus and the cytoplasm, suggesting that they might participate in the transport of selected mRNA. Both proteins bind constitutively to TNF-α mRNA in unstimulated and stimulated macrophages[22,23]. TIA-1 has multiple roles in the regulation of TNF-α expression, which may be negative or positive depending on the context. More TNF-α mRNA is found associated with polysomes in peritoneal macrophages isolated from TIA-1-null mice compared with control mice, demonstrating its function in transcript-specific translational silencing[22]. The inhibitory mechanism remains to be determined, but may involve sequestration in cytoplasmic mRNA storage depots known as stress granules, which contain TIA-1 and TIAR[33,34]. Moreover, Phillips et al. showed that TIA-1 and TTP function as arthritis-suppressor genes. TIA-1$^{-/-}$ mice develop mild arthritis, TTP$^{-/-}$ mice develop severe arthritis and TIA-1$^{-/-}$TTP$^{-/-}$ mice develop very severe arthritis[35]. However, it is surprising to note that LPS-activated TIA-1$^{-/-}$TTP$^{-/-}$ macrophages secrete

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less TNF-α protein than do either TIA-1^{-/-} or TTP^{-/-} macrophages[35]. In these mice, arthritogenic cytokines may be produced by neutrophils that accumulate in the bone marrow and peripheral blood. However, little is known about the expression or the function of these proteins in neutrophils.

mi-RNA

mi-RNA can regulate cytokine expression either by binding directly to a target sequence in a cytokine mRNA or by regulating RNA-binding protein clusters indirectly. In mechanistic terms, miRNA pairs with partially complementary sequences on target mRNA and regulates stability and/or translation. Changes in their expression during the response to extracellular signals allow miRNA to regulate these processes. Recent studies have identified miRNA as a critical regulator of immune responses including inflammation. For example, up-regulation of miR-155 in LPS-activated macrophages resulted in enhanced translation of TNF-α mRNA[36,37]. In contrast, miR-125 appeared involved in the post-transcriptional repression of TNF-α mRNA and induced down-regulation of TNF-α production[37]. Moreover, transgenic mice expressing recombinant miR-155 produce higher levels of TNF-α when exposed to LPS and are hypersensitive to LPS-induced septic shock, suggesting that the TNF-α-stimulating role of miR-155 may have a major effect in pathology. In fact, abnormal expression of miRNA in rheumatoid arthritis patients has been reported recently, with miR-155 and miR-146 expression in synovial tissues and synovial fibroblasts isolated from these patients being higher than that in healthy controls. Although a direct binding site for miR-155 on the TNF-αmRNA has not been identified, miR-155 might have a stabilizing function, since miR-155-deficient B cells fail to produce measurable amounts of TNF-α. Furthermore, a role for

miR-155 in TNF-α mRNA stabilization has been shown in HEK293 cells, and miR-155-transgenic mice have increased levels of circulating TNF-α after LPS injection.

It appears that miRNA might function together with RNA-binding proteins to regulate mRNA expression through ARE. TNF-α mRNA generally contain long AREs. A recent study has shown that miR-221, miR-579 and miR-125b are expressed following the induction of a state of LPS tolerance, during which TNF-α mRNA is degraded. In addition, miR-221 has been found to associate with TTP and to accelerate TNF-α mRNA decay, while miR-579 and miR-125b seems to block TNF-α translation, possibly through recruitment of the translational inhibitor TIAR[38,39]. However, it should also be noted that some of these effects could be mediated directly by up-regulation of miR-125b expression, which might destabilize TNF-α by direct binding.

On the other hand, fibroblast-like synoviocytes residing in the joint space also play a crucial role in rheumatoid arthritis. While fibroblast-like synoviocytes secrete no TNF-α, it is intriguing to note that they express TNF-α mRNA in response to LPS. Blocking miR346 allows TNF-α expression in activated fibroblast-like synoviocytes. In addition, miR-346 transfection in LPS-activated THP-1 cells leads to increased TTP mRNA expression and inhibits TNF-α secretion, suggesting that miR-346 controls TNF-α synthesis by regulating TTP expression[40].

p38 MAP Kinase Pathways

The ability of RNA-binding proteins to interact with cytokine mRNA, and hence regulate cytokine expression, is also controlled through post-translational modification. Such modification is mediated through kinases and phosphatases that may change the binding efficiency of RNA-binding proteins to the ARE sites within mRNA. As mentioned above, some

MAP kinases control cytokine mRNA stability via ARE.

Kontoyiannis et al. demonstrated that when TNF-α ARE sequences were deleted from the mouse genome, the resulting mutant mRNA was no longer responsive to translational modulation by p38 kinases and Jun N-terminal kinase[16]. Signalling mediated by p38/MK-2 is required for TTP phosphorylation, which in turn promotes TTP sequestration, an event that is partially dependent on binding to members of the family of regulatory proteins known as 14-3-3. These proteins inhibit TTP activity by preventing binding to the stress granules in which the mRNA is stored and triaged. Down-regulation of TTP thus leads to increased cytokine production, since it can no longer bind to ARE and destabilize mRNA[31].

MAP kinase increases cytoplasmic localization of HuR and thus participates in the stabilization and/or translation of TNF-α, interleukin-8 and COX-2 mRNA, among others[41]. It is interesting that HuR also stabilizes mRNA and facilitates translation of MAPK phosphatase-1 (MKP-1)[42], an enzyme that dephosphorylates and inactivates extracellular signal-regulated MAP kinase, c-JNK and p38. In this model, MAP-kinase-activated HuR stabilizes and enhances the translation of stress-response mRNA, including that of MKP-1, which eventually leads to MAP kinase shut-off. To date, MK-2 is the only kinase that has been shown to be involved in regulating specific messages through direct phosphorylation of RNA-binding proteins. MK-2 is activated by p38 MAPKα/β and is necessary for LPS-induced TNF-α biosynthesis in murine macrophages[43]. It has been reported that MK-2 phosphorylates three RNA-binding proteins that associate with TNF-α mRNA, TTP[44], HuR[45] and hnRNP-A1[46].

A recent study of macrophages has shown that translation of the TNF-α precursor requires expression

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of HuR together with either activity of the p38 MAPK/MK-2 pathway or absence of TTP. Phosphorylation by MK-2 decreases the affinity of TTP for ARE, inhibits its ability to replace HuR and allows HuR-mediated initiation of TNF-α mRNA translation. The phosphorylation-regulated TTP/HuR exchange on target mRNA molecules thus provides a reversible switch between unstable/non-translatable and stable/efficiently translated mRNA[47].

Conclusion

Post-transcriptional mechanisms impose a series of flexible controls that adjust the abundance of TNF-α mRNA and its rate of translation, which together result in a tailored TNF-α-driven response to specific external signals. These post-transcriptional controls consist of signalling networks converging on RNA-binding proteins and miRNAs, which in turn target a code of secondary or tertiary ribonucleotide structures located on the TNF-α mRNA. While increased synthesis of TNF-α is associated with the development of rheumatoid arthritis, little is known about the translational mechanism that controls its synthesis in the neutrophils that play an important role in rheumatoid arthritis pathogenesis, contributing directly to acute and chronic inflammation and immune dysregulation. Since neutrophils have been identified as essential components of the inflammatory process in animal models of inflammatory arthritis, better understanding of the intracellular proteins and signalling pathways that regulate TNF-α biosynthesis is crucial to the development of novel anti-TNF-based therapies for rheumatoid arthritis patients.

Acknowledgements

Abbreviations list

ARE, adenosyl-uridyl-rich element; hnRNP, heterogeneous nuclear ribonucleoprotein; HuR-A1, Hu antigen R; LPS, lipopolysaccharide; miRNA, micro-RNA; MKP-1, MAPK phosphatase-1; TIA-1, T-cell intracellular Ag; TIAR, TIA-1-related protein; TLR, toll-like signalling receptor; TNF-α, tumour necrosis factor-alpha; TTP, tristetraprolin.

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