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TNFR signalling and its clinical implications

Wen-Yi Tseng [a,b,*], Yi-Shu Huang [a], Hsi-Hsien Lin [c,d], Sheu-Fen Luo [e], Fiona McCann [a], Kay McNamee [a], Felix Clanchy [a], Richard Williams [a]

[a] Kennedy Institute of Rheumatology, University of Oxford, OX3 7FY Oxford, UK
[b] Division of Rheumatology, Allergy and Immunology, Chang Gung Memorial Hospital-Keelung, Keelung, Taiwan
[c] Department of Microbiology and Immunology, College of Medicine, Chang Gung University, Taoyuan, Taiwan
[d] Department of Anatomic Pathology, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
[e] Division of Rheumatology, Allergy and Immunology, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan

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ABSTRACT

Tumour necrosis factor-α (TNF-α) is a highly pleiotropic cytokine with effects on multiple pathological and physiological functions via two distinct receptors, TNFR1 and TNFR2. Much of the pro- inflammatory action of TNF-α is mediated by TNFR1 whereas TNFR2 is thought to play an immunoregulatory and tissue protective role. Anti-TNF- α biologics have been extremely successful in treating a number of immune mediated pathologies, including rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis and inflammatory bowel disease. However, anti-TNF therapy has been shown to induce systemic lupus erythematosus and psoriasis in some patients, and to be deleterious in multiple sclerosis. It is hypothesized that these paradoxical effects of anti-TNF-α are due to inhibition of TNFR2 signalling. In this review, we will focus on the biology and pathophysiologic role of TNF-α and on the therapeutic implications of targeting TNF-α receptor signalling.

1. Introduction

Tumour necrosis factor (TNF) is a potent inflammatory mediator exerting effects on many different pathological and physiological functions. The discovery of TNF can be traced back over a century ago, with the observation by P. Brunes that some cancer patients experienced tumour regression following acute bacterial infection. This finding led to the practice by William B. Coley [1] of injecting cancer patients with bacteria or bacterial products, referred to as Coley's toxin. In 1962, O'Malley et al. reported tumour necrotizing activity in the serum obtained from mice after injection of *Serratia marcescens* polysaccharide [2]. The name "TNF" was first used by Carswell et al. to name the substance in the serum of mice treated with endotoxin, which resulted in haemorrhagic necrosis of tumours [3]. In 1984 and 1985, two proteins that caused lysis of tumour cells were purified, structurally identified and cDNA cloned [4–6]. They were named TNF-α and TNF-β. These proteins showed around 50% sequence homology and interacted with the same membrane receptors but were produced from different cells and exhibit different physiological functions [4–6]. Beutler et al. reported that a high degree of homology between mouse cachectin and human TNF-α [7]. The advancement in our understanding of TNF-α, coinciding with improvements in molecular biology capabilities, has resulted in the generation of recombinant TNF-α (rTNF-α) which led to investigations into the clinical utility of TNF-α.

TNF-α was first identified as a nonspecific anti-tumour therapy. Early studies demonstrated the efficacy of utilizing purified TNF-α against various kinds of murine and human tumours heterotransplanted into nude mice [8]. However, all phase I clinical trials of intravenous, subcutaneous or intramuscular-administered rTNF-α showed symptoms of toxicity, including fever, chills, headache, fatigue, dyspnea, tachycardia and hypotension, without significant clinical efficacy in advanced cancer patients [9–12]. Although TNF-α was not shown to be an effective treatment for cancer, several studies indicated that TNF-α was a potent mediator of inflammation via induction of IL-6 [13,14]. Subsequently, in a series of key experiments it was shown that blockade of TNF-α in cultures of synovial cells from rheumatoid arthritis (RA) patients abrogated the expression of IL-1 and other pro-inflammatory cytokines, suggesting that TNF-α was pivotal in driving the production of multiple mediators of inflammation [15]. The importance of TNF-α in the pathogenesis of RA was confirmed in clinical trials in which intravenous administration of chimeric anti-TNF-α mAb

* Corresponding author at: Kennedy Institute of Rheumatology, University of Oxford, OX3 7FY Oxford, UK.
E-mail address: wen-yi.tseng@stx.ox.ac.uk (W.-Y. Tseng).

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(infliximab, Remicade®) caused clear reductions in the level of disease activity and radiographic progression [16–18]. Similar findings were subsequently reported for soluble TNF-α receptor-Fc fusion protein (etanercept, Enbrel®) [19–21]. Anti-TNF-α therapy was approved for treatment, in combination with methotrexate, of RA patients in 1998. In addition to RA, anti-TNF-α therapy has now been approved for the treatment of ankylosing spondylitis (AS), psoriasis, psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA), inflammatory bowel disease (IBD), and most recently, hidradenitis suppurativa and noninfectious intermediate and posterior uveitis and panuveitis [22,23]. However, clinical trials with anti-TNF-α therapy in multiple sclerosis (MS) patients resulted in disease exacerbation [24,25]. Moreover, it has been reported that the use of anti-TNF-α therapy in RA resulted in the development of autoimmune disease of systemic lupus erythematosus (SLE) and MS [26,27]. The paradoxical effects of anti-TNF-α therapy suggest that TNF-α plays both proinflammatory and regulatory roles in the immune system. In this review, we will focus on the biology and pathophysiologic role of TNF-α and on the therapeutic implications of modulating TNF-α receptor signalling.

2. TNFR1 and TNFR2 signalling

TNF-α is a pleiotropic pro-inflammatory cytokine, mainly produced by activated monocytes/macrophages, but also by various cell types such as NK cells, T lymphocytes and eosinophils in response to various stimuli [28]. TNF-α is initially synthesized as a type II transmembrane protein of 233 amino acids, then expressed on the cell surface as a trimer. Subsequent cleavage by TNF-converting enzyme (TACE, also named ADAM17) liberates the trimer into the circulation. Both the membrane form of TNF-α (mTNF-α) and the soluble form of TNF-α (sTNF-α) exert physiologic functions by binding to two structurally and functionally distinct receptors on target cells, TNF receptor 1 (also named as TNFR1, CD120a, p55 and TNFRSF1A) and TNF receptor 2 (also named as TNFR2, CD120b, p75 and TNFR12A) on target cells.

TNFR1 is ubiquitously expressed, bears a cytoplasmic death domain, and is activated by both mTNF-α and sTNF-α [29]. The death domain enables TNFR1 to recruit TNFR1 associated death domain protein (TRADD), which mainly leads to apoptosis and inflammation [30]. By contrast, TNFR2 is expressed on a restricted range of cell types including activated $CD4^+$ and $CD8^+$ lymphocytes, endothelial cells, astrocytes, oligodendrocytes, thymocytes, myocytes, and human mesenchymal stem cells [31–37], and is preferentially activated by mTNF-α [29]. Due to the lack of a death domain, TNFR2 recruits TNFR associated factor 1 (TRAF1) and TRAF2 rather than TRADD [30,38,39]. In contrast to TNFR1-TRADD signalling, TNFR2 signalling through TRAF1 and TRAF2 mediates a homeostatic effect, including cell survival and tissue regeneration [40]. However, further studies have revealed a degree of receptor crosstalk and overlapping function between TNFR1 and TNFR2, which seems to depend on multiple factors, such as cell type, intracellular or extracellular environment, stimuli and age [41,42].

Upon engagement by TNF-α, TNFR1 translocates to lipid rafts in the plasma membrane and forms a homotrimer [43,44]. The binding of TNF-α to TNFR1 induces a conformational change in the cytoplasmic death domain of TNFR1, which results in the recruitment of TRADD and receptor-interacting serine/threonine-protein kinase I (RIPKI) [38,45,46]. The co-localisation of TFNR1, TRADD and RIPKI initiates the assembly of distinct complexes, named complexes I, IIa, IIb and IIc, which leads to activation of distinct downstream signalling pathways [47,48]. The formation of these three complexes is mainly determined by the ubiquitination status of RIPK1. Complex I is composed of TRADD, RIPK1, TRAF2 or TRAF5, cellular inhibitor of apoptosis protein 1 (cIAP1) or cIAP2 and the linear ubiquitin chain assembly complex (LUBAC) [38,45,47,49–51]. Initially, both TRAF2/5 and cIAP1/2 are E3 ubiquitin ligases that mediate K63-linked ubiquitination of RIPKI [52–54]. Subsequently, the LUBAC complex, which consists of haeme-oxidized IRP2 ubiquitin ligase 1 (HOIL1), HOIL1-ineracting protein (HOIP) and SHANK-associated RH domain-inertracting protein (SHARPIN), attaches an M1-linked polyubiquitin chain to RIPK [50,55–57]. Both K63- and M1-linked polyubiquitination events stabilize complex I and facilitate further signalling. Ubiquitin chains attached to RIPK1 enable the recruitment and activation of two signalling complexes, transforming growth factor (TGF)-activated kinase I (TAKI) complex and the inhibitor of κB (IκB) (IKK) complex [50,55]. The TAKI complex, which is composed of TAKI, TAKI-binding protein 2 (TAB2) and TAB3, phosphorylate mitogen-activated kinase (MAPK) and consequently lead to the activation of the c-JUN N-termianl kinase (JNK), p38 and AP1 transcription factor [58,59]. The IKK complex, comprising nuclear factor κB (NFκB) essential modulator (NEMO), IKK subunit-α (IKKα) and IKKβ, activate NFκB pathway signalling [60,61]. Induction of NFκB and AP1 target genes plays an indispensable role in inflammation, host defense, cell proliferation and survival [47].

In contrast, the formation of complex IIa and IIb depends on non-ubiquitinated RIPK1. For the formation of complex IIa, the attached K63- and M1- linked polyubiquitin chain are removed from RIPK1 in complex I by cylindromatosis (CYLD) and result in dissociation of the deubiquitinated RIPK1 from membrane bound complex I [62–64]. The released deubiquitinated RIKP1 interacts with cytosolic TRADD, FAS-associated death domain protein (FADD), pro-caspase 8 and the long isoform of FLICE-like inhibitory protein ($FLIP_L$) to form complex IIa [65,66]. Alternatively, complex IIb is formed when the RIPK1 is not ubiquitinated due to the depletion or degradation of cIAPs [52]. The non-ubiquitinated RIPK1 dissociates from membrane bound complex I and interacts with RIPK3, pro-caspase 8 and $FLIP_L$ to from complex IIb. Both complexes IIa and IIb generate active caspase 8 from pro-caspase 8 and lead to activation of the downstream caspase cascade and thus induce cell death via apoptosis. Concurrently, the deubiquitinated RIPK1 and RIPK3 must be cleaved by the pro-caspase 8- $FLIP_L$ heterodimer or active caspse 8 to prevent cells from necroptosis [65,67–70]. The formation of complex IIc is similar to complex IIa and complex IIb formation in that the released deubiquitinated or non-ubiquitinated RIPK1is caused by deubiquitination mediated by CYLD or depletion of cIAPs. However, in some circumstances, RIPK1 and RIPK3 cannot be cleaved due to inactivation of caspase and aggregate to form complex IIc (also named as necrosome). Complex IIc activates mixed lineage kinase domain-like protein (MLKL) and leads to the induction of necroptosis [38,46,71]. In contrast to apoptosis which is a form of highly controlled programmed cell death, necroptosis results in plasma membrane rupture, which leads to leakage of intracellular contents and local inflammation [38,39] (see Fig. 1).

TNFR2 lacks TRADD, but instead binds to TRAF1 or TRAF2 to recruit cIAP1 or cIAP2. The binding of TRAF2 to TNFR2 is much weaker in comparison with that of TRAF2 to TRADD [72]. The aggregation of TRAF1/2 and cIAP1/2 triggers the formation of complex I and downstream MAPK and NFκB signalling. TNFR2-TRAF signalling mediates a homeostatic effect including tissue generation, cell proliferation and cell survival [40]. The interaction between TNFR1 and TNF2 has not been fully elucidated. The difference of binding affinity between TRAF2-TNFR2 and TRAF2-TRADD suggests that TNFR2 may have a regulatory effect on TNFR1 signalling in the same cell [71–73] (see Fig. 1).

Previously, it has been proposed that TNFR2 is required for TRAF2 degradation, leading to activation of the alternative NFκB pathway and contributing to MAPK and classical NFκB signalling.

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