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TNFα in the regulation of Treg and Th17 cells in rheumatoid arthritis and other autoimmune inflammatory diseases

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ABSTRACT

TNFα is a principal pro-inflammatory cytokine vital for immunity to infections. However, its excessive production is involved in chronic inflammation and disease pathology in autoimmune diseases. Evidence for its pathogenic role is validated by the fact that its neutralisation by therapeutic agents *in vivo* is beneficial in ameliorating disease and controlling symptoms. Paradoxically, however, treatment with TNFα inhibitors can either have no clinical effects, or even exacerbate disease in some patients. The explanation for such contradictory outcomes may lay in how and which downstream signalling pathways are activated and drive disease. TNFα causes its effects by binding to either or both of two membrane-bound receptors, TNFR1 and TNFR2. Engagement of the receptors can induce cell death or cell proliferation.

T cells both produce and respond to TNFα and depending on whether the cytokine is membrane-bound or soluble and the level of expression of its two receptors, the biological outcome can be distinct. In addition, polymorphisms in genes encoding TNFα and T cell signalling proteins can significantly impact the outcome of TNFα receptor engagement. Early studies revealed that effector T cells in patients with rheumatoid arthritis (RA) are hyporesponsive due to chronic exposure to TNFα. However, recent evidence indicates that the relationship between TNFα and T cell responses is complex and, at times, can be paradoxical. In addition, there is controversy as to the specific effects of TNFα on different T cell subsets. This review will summarise knowledge on how TNFα modulates T cell responses and the effect of engaging either of its two receptors. Furthermore, we discuss how such interactions can dictate the outcome of treatment with TNFα inhibitors.

1. Introduction

TNFα is a 233 amino acid protein produced by macrophages, dendritic cells (DCs), T cells, B cells, endothelial cells, mast cells and neural cells [1,2] in response to infections and/or inflammatory stimuli. It plays a key role in initiating immunity to pathogens but is also associated with chronic inflammation and tissue damage in several inflammatory autoimmune diseases [3–5]. This review will discuss how TNFα stimulates T cell sub-populations and how this promotes, exacerbates or modulates autoimmune diseases.

2. TNFα signals through two receptors

When produced, TNFα is transported to the cell membrane to be expressed as a membrane-associated trimer. Membrane TNFα may subsequently be cleaved by TNFα converting enzyme (TACE) and shed as a trimer into the circulation [6]. Both the membrane form (mTNFα) and the shed form, or soluble form (sTNFα), are biologically active. T cells are important producers of TNFα and studies using animal models have revealed that T cell-derived TNFα is vital in initiating protective immunity against infections [3]. TNFα derived from T cells, unlike TNFα from other cell sources, often remains as a membrane form and functions via cell-cell contacts [7]. TNFα binds two membrane receptors, TNF receptor 1 (TNFR1), a 55 kDa protein and TNFR2, 75 kDa protein (Figs. 1 and 2). TNFR1 is ubiquitously-expressed while TNFR2 has a restricted expression pattern on a few cell types, notably immune cells. T cells, for

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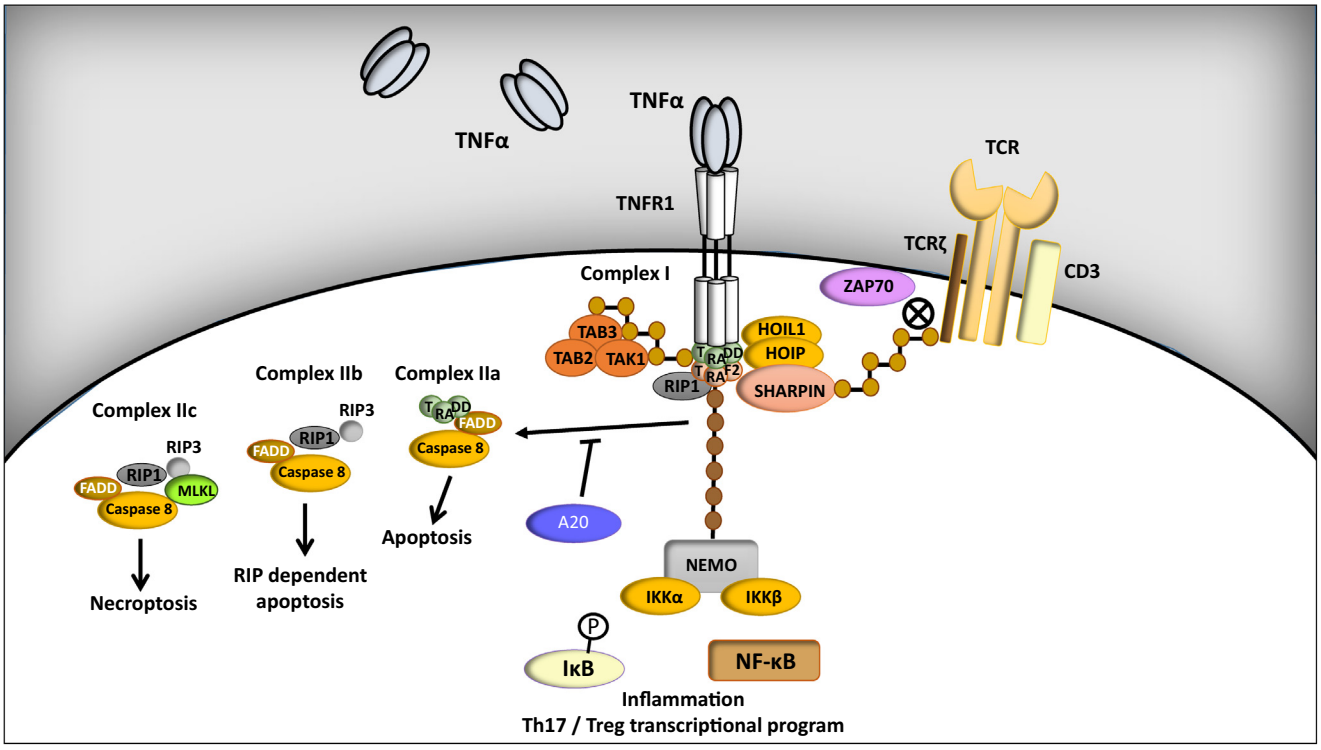

Fig. 1. Signalling of TNFα downstream of its receptor 1 (TNFR1). TNFα binding to TNFR1 leads to the activation of complex I leading to cell necroptosis. Activation of complex I involves proteins TADD, RIP1, TRAF2, cIAP1 and LUBAC. RIP1 mediate K63-linked ubiquitination and activation of the TAK1 complex. The TAK 1 complex consists of TAK1, TAB2 and TAB3. The activation of TAK1 triggers the signalling pathways MAPK, JNK, p38 and AP1. Both RIP1/cAIP and LUBAC facilitate K48 ubiquitination of the IKK complex. This leads to its degradation, phosphorylation of the NF-κB inhibitor IκB and NF-κB translocation to the nucleus. NF-κB induces cell specific-transcriptional programs in effector T cells (Teffs), Th17 cell and Tregs. There is a direct link between TNFR1 and the T cell receptor (TCR) as one of components of LUBAC, Sharpin, can ubiquitinate TCRζ (K63-linked) in Tregs leading to its disassociation from ZAP70 and, ultimately, cell proliferation. If components of complex I are limiting, complex IIa, IIb or IIc can be activated. Activation of complex IIa and IIb leads to apoptosis. Activation of complex IIc leads to necroptosis. Polymorphism in gene for the ubiquitin-editing enzyme A20 (*TNFAIP3*) is associated with RA. This polymorphism appears to influence activation of complexes II.

example, express both TNFR1 and TNFR2 [8]. TNFR1 can be triggered fully by both the membrane and soluble forms of TNFα whereas most reports indicate that TNFR2 is efficiently activated only by the membrane form. However, there is evidence that sTNFα bound to TNFR2 may be passed onto TNFR1 to induce biological effects [9].

The binding of TNFα to its two structurally-different receptors activates distinct but partially overlapping signalling pathways and, therefore, induces different responses. This is reflected in the activation of different downstream intracellular protein complexes inside cells (Figs. 1 and 2). Engagement of TNFR1 primarily induces cell death by apoptosis or necrosis, mediated mostly by the activation of caspases via its cytoplasmic death domain. TNFR2, in contrast, lacks a death domain and, instead, promotes cell proliferation and homeostatic activities mainly through the nuclear factor 'kappa-light-chain-enhancer' of activated B cells (NF-κB). Many studies have indicated that TNFR2 is the most important receptor for TNFα-dependent regulation of T cells, especially regulatory T cells (Tregs) [10]. However, TNFR1 is also important for the development of effector T cells and, indeed, is expressed on both Tregs and Th17 cells [11,12]. Recent studies have highlighted the importance of ubiquitination in the regulation of TNFα signalling downstream of TNFR1 and TNFR2 in T cells. Furthermore, genome-wide association studies (GWAS) have revealed that genes encoding TNFAIP3 (also called A20) and TRAF1, which are associated with the TNFRs and involved in ubiquitination, are associated with susceptibility to autoimmune diseases [4]. This section will briefly review known signalling pathways activated downstream of TNFR1 and TNFR2.

TNFR1-induced NF-κB signalling regulates cell survival but also initiates the activation of caspases that ultimately trigger cell death. The ubiquitination of various downstream signalling proteins determines whether TNFR1 engages complex I-dependent cell survival or complex II-dependent apoptosis. Thus, ubiquitination is no longer regarded a process solely involved in protein degradation but is known to also confer signal transduction. Ubiquitination by joining ubiquitin residues using different lysine (K) amino acid residues on the small protein confer different effects. Hence, generating ubiquitin chains by joining at lysine 48 (K48) mediates transport of the ubiquitinated protein to the proteasome for subsequent degradation. Ubiquitination generating chains linked at K63, on the other hand, regulates a variety of nonproteolytic cellular functions [13,14]. TNFR1 has an intracellular domain called death domain which recruits TNFR1-associated death domain (TRADD) protein. Downstream of TRADD, protein complexes I, IIa, IIb and IIc are activated. Activation of complex I induces inflammation, tissue degeneration and mediates host immune defences. Complex I consists of TRADD, receptor-interacting serine/threonine-protein kinase 1 (RIP1), TNF receptor-associated factor 2 (TRAF2), cellular inhibitor of apoptosis (cIAP1) and the linear ubiquitin chain assembly complex (LUBAC, Fig. 1) [14–16]. The E3 ligase activity of cIAPs is required for the Haem-oxidized IRP2 ubiquitin ligase-1 (HOIL-1) recruitment to complex I. LUBAC consists of the K48-polyubiquitin specific E3 ubiquitin ligase HOIL-1, the E3 ubiquitin ligase HOIL-1L interacting protein (HOIP) and Shanks associated RH domain interacting protein (Sharpin). LUBAC ubiquitinates several proteins including IKKβ and T cell receptor ζ chain (TCRζ). K63-linked ubiquitination by RIP1 builds a scaffolding ubiquitin complex, TAK1 complex, which

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