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Survey

Regulation and dysregulation of tumor necrosis factor receptor-1

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ABSTRACT

TNF is an essential regulator of the immune system. Dysregulation of TNF plays a role in the pathology of many auto-immune diseases. TNF-blocking agents have proven successful in the treatment of such diseases. Development of novel, safer or more effective drugs requires a deeper understanding of the regulation of the pro-inflammatory activities of TNF and its receptors. The ubiquitously expressed TNFR1 is responsible for most TNF effects, while TNFR2 has a limited expression pattern and performs immune-regulatory functions. Despite extensive knowledge of TNFR1 signaling, the regulation of TNFR1 expression, its modifications, localization and processing are less clear and the data are scattered. Here we review the current knowledge of TNFR1 regulation and discuss the impact this has on the host.

Contents

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1. TNFR1, the major receptor of TNF

TNF is a type II transmembrane glycoprotein consisting of three monomers with a typical β-jellyroll structure. Each subunit consists of two packed β-sheets of five antiparallel β-strands with three additional β-strands in the N-terminal part (Fig. 1). The first 76 amino acids form a highly conserved hydrophobic sequence that anchors the precursor polypeptide in the membrane. This immature protein (transmembrane pro-TNF) has a molecular mass of 26 kDa and is proteolytically cleaved, mainly by the metalloprotease TNFα converting enzyme (TACE or ADAM17), to a 17-kDa active unit [1]. Also other proteases, such as ADAM10 [2], MMP7 [3] and MMP13 [4], have been shown to cut pro-TNF and generate soluble TNF. Soluble TNF is a homotrimer with a molecular mass of 52 kDa. The **TNF** protein structure and its interaction with TNFR1 have been described in great detail from high resolution crystals. The homotrimer looks like a triangular cone or bell in which the three subunits are arranged edge to face [5]. The receptor binding sites of TNF are located in the lower half of the triangular cone, in the groove between two subunits [6].

TNF binds with high affinity to two type I transmembrane receptors: TNFR1 (CD120a), which is activated by both soluble TNF (sTNF) and transmembrane TNF (tmTNF), and TNFR2 (CD120b), which is activated mainly by tmTNF. Most of the biological activities of TNF are initiated by binding to TNFR1 [7].

Mouse **TNFR1** has a length of 454 amino acids (AA), of which the 21 N-terminal AAs are a signaling peptide, followed by an extracellular domain (ECD) of 191 AA, a helical transmembrane domain (TMD) of 23 AA, and an intracellular domain (ICD) of 219 AA (Fig. 2). The extracellular regions of TNFR1 and TNFR2 are structurally highly homologous. The N-terminal ECD contains two extracellular topological domains (AA 22–43 and AA 197–212) and four cysteine rich domains (CRD) at AA 44–82, AA 83–125, AA 126–166 and AA 167–196, each of which contains six cysteines. Transmembrane TNFR1 is also a substrate of TACE. The major TNFR1 cleavage site is the spacer region close to the transmembrane domain between N202 and V203 [8]. There is no significant homology in the intracellular region between TNFR1 and TNFR2, indicating that these receptors activate distinct signaling pathways. TNFR1 contains a cytoplasmic death domain (DD) which is a homophilic protein–protein interaction region of 86 AA (356–441) required for TNF-induced apoptosis, and an N-SMASE activation domain (NSD) spanning an 11-AA motif N-terminal to the DD.

The pre-ligand assembly domain (PLAD) is a homophilic protein–protein interaction motif located in CRD1 and plays an important role in both TNFR1 and TNFR2 signaling pathways by assisting in the assembly of the receptor complex required for TNF binding. It has been proposed that PLAD-mediated homomultimer formation stabilizes CRD2 in a conformation necessary for high affinity ligand binding [9]. In autoimmune diseases, this PLAD region might serve as a target to prevent TNF signaling [10].

Binding of TNF to TNFR1 results in trimerization of the pre-existing receptor complexes and clustering of the intracellular death domains. Subsequently, the adapter molecule TRADD binds by interaction of death domains (DD) of TRADD and TNFR1. TRADD acts as a platform adapter that can recruit TNFR associated factor 2 or 5 (TRAF2/5), cellular inhibitor of apoptosis 1 and 2 (cIAP1/2) and receptor interacting protein 1 (RIP1) to form the membrane-bound **complex I** [11]. This allows cIAP to K63-ubiquinate RIP1 and TRAF2/5, leading to activation of the inhibitor of κB (I-κB) kinase complex (IKK) [12]. Additionally, linear ubiquitination of IKKγ or NEMO by the LUBAC complex stabilizes the IKK complex [13]. Phosphorylation of I-κB by IKK ensures I-κB K48-ubiquitination and degradation by the proteasome and consequent activation of NF-κB. Activation of AP-1 involves a phosphorylation cascade mediated by the mitogen activated protein (MAP) kinases. These kinases are responsible for activating c-Jun N-terminal kinases JNK1, 2 and 3 and p38, leading to activation and nuclear translocation of c-Fos and c-Jun [11]. Hence, complex I stimulates pathways leading to activation of NF-κB and AP-1 and induction of pro-inflammatory and anti-apoptotic genes. One such anti-apoptotic gene encodes c-FLICE inhibitory protein (c-FLIP), which

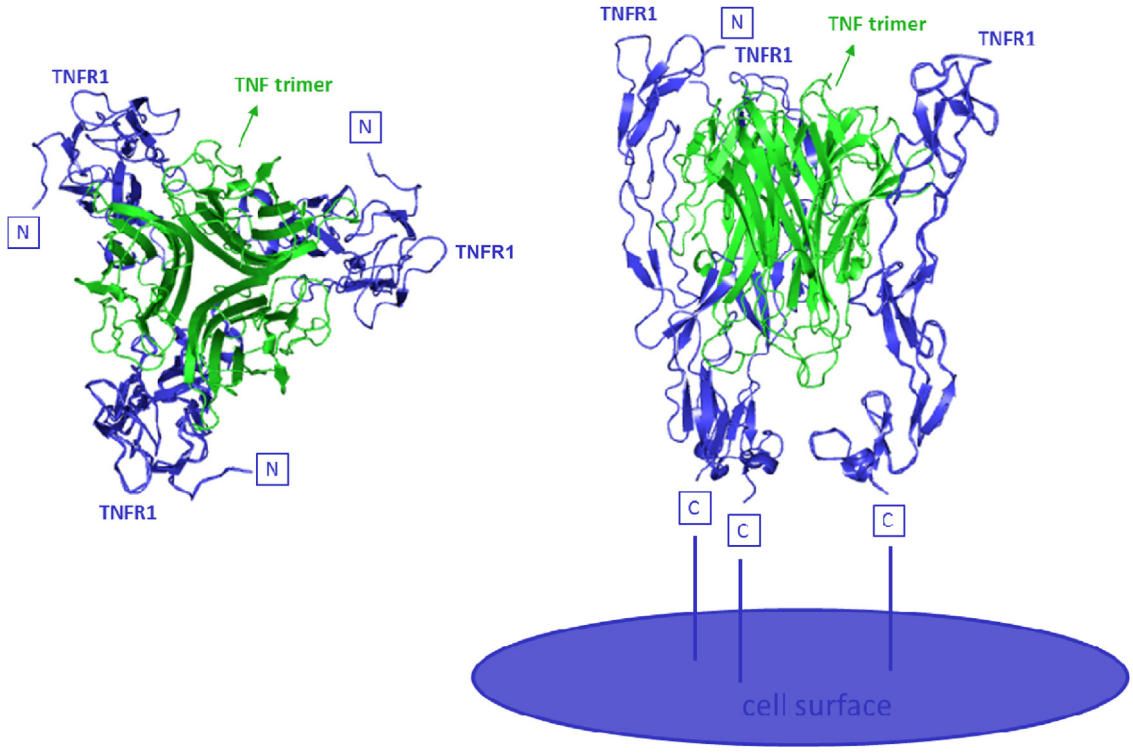

Fig. 1. Crystal structure of TNF (PDB 1TNF in green) and binding to its receptor TNFR1 (PDB 1EXT in blue). Top view is on the left and side view on the right [171,172].