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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

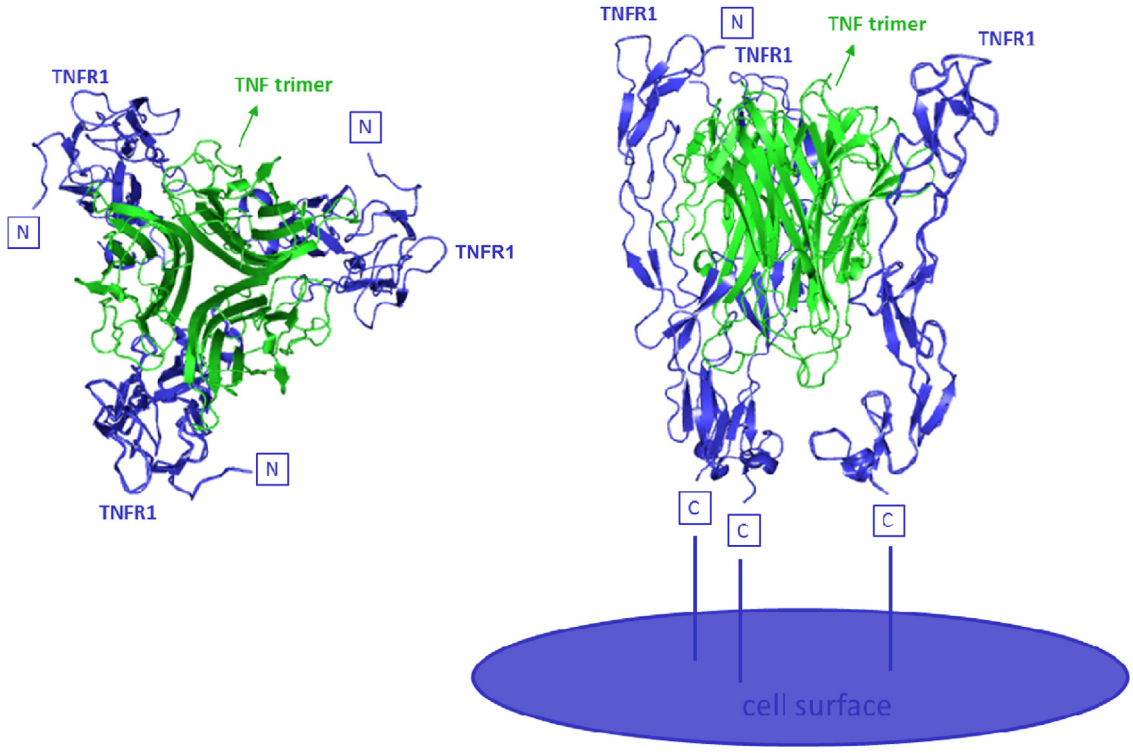

Fig. 1. Crystal structure of TNF (PDB 1TNF in green) and binding to its receptor TNFR1 (PDB 1EXT in blue). Top view is on the left and side view on the right [171,172].

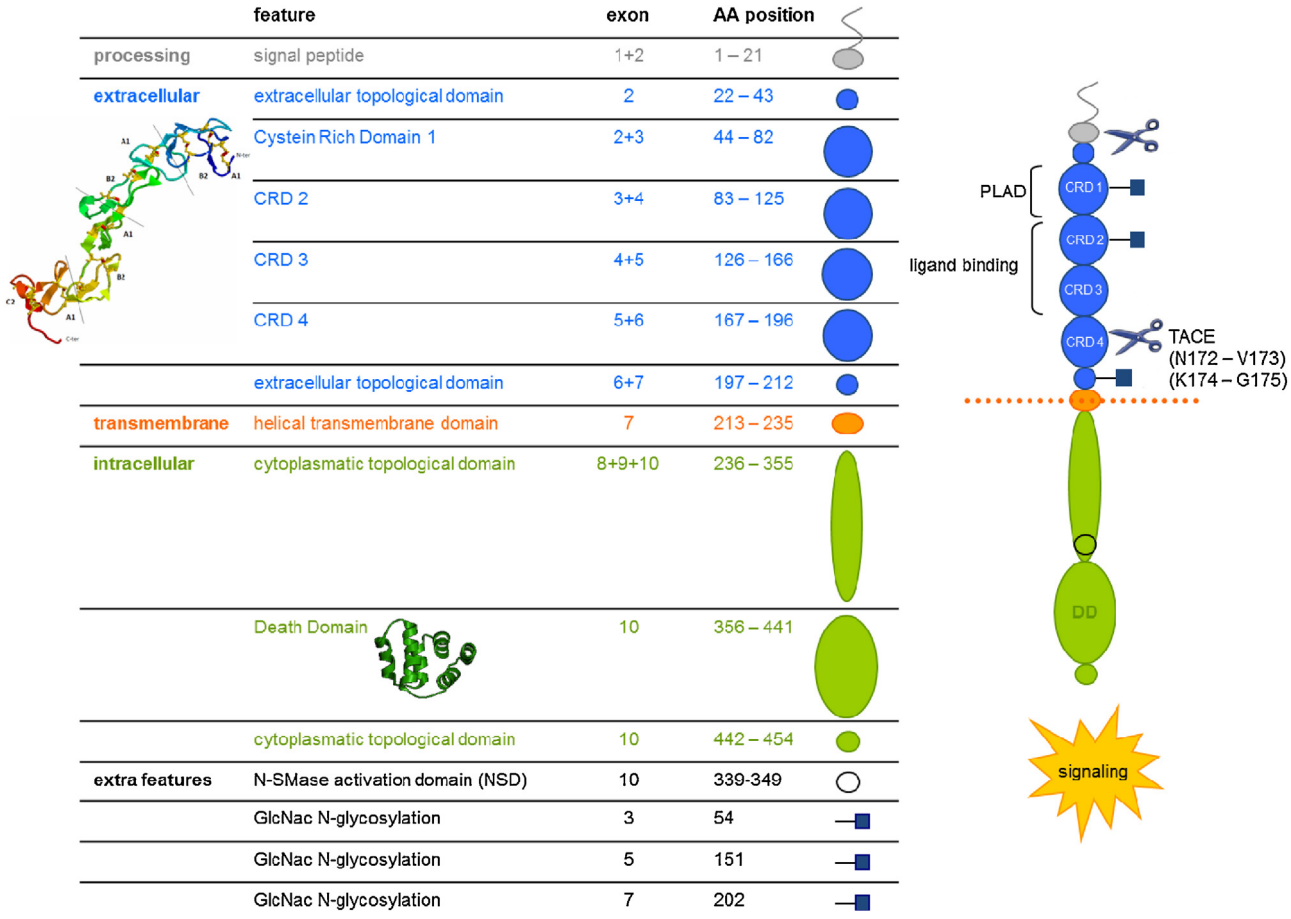

Fig. 2. Representation of TNFR1 (UniProtKB P25118). For detailed description see text.

is a specific inhibitor of caspase 8 (an essential molecule in the apoptotic pathway) [11]. However, prolonged JNK activation can also induce pro-apoptotic proteins such as Itch, which can mediate c-FLIP degradation [14]. However, the duration of NF-κB activation is limited by several feedback mechanisms, such as the induction of I-κB, CYLD and A20. CYLD, a protease that specifically cleaves K63-ubiquitin chains, de-ubiquitinates TRAF2, thereby inhibiting the recruitment of TAB/TAK and activation of IKK [15], and A20 deactivates RIP1 by removing the K63-ubiquitin chain and adding a K48-ubiquitin chain [16]. Sustained MAPK activation is prevented by MAPK phosphatases such as MKP-1. However, TNF-induced reactive oxygen species (ROS) can disturb some of the feedback systems, for example by oxidizing MKP-1 [17].

Upon endocytosis of complex I, TRADD dissociates from TNFR1 and associates with Fas-associated protein with death domain (FADD) to form the intracellular located **complex II**. De-ubiquitination of RIP1 leads to recruitment and autocatalytic cleavage of pro-caspase 8, thereby initiating apoptosis [18]. However, in conditions where caspase 8 is inhibited, RIP3 can be recruited and RIP1 and RIP3 become phosphorylated by auto phosphorylation or cross phosphorylation, leading to necroptosis, a regulated form of necrosis. Necroptosis causes rapid plasma membrane permeabilization with release of reactive oxygen species (ROS) and exposure of damage-associated molecular patterns (DAMPs), which provide strong stimulation of the immune system [19].

2. The biological significance of TNFR1

TNF signals through two distinct receptors, TNFR1 and TNFR2. These receptors initiate diverse important effects, including proliferation, differentiation, migration, inflammation and cell death [20]. The pro-inflammatory and pathogen-clearing activities of TNF are mediated mainly through activation of TNFR1, which is a strong activator of NF-κB, while TNFR2 may be more responsible for suppression of inflammation [21].

Several groups generated **TNFR1 deficient mice** by gene targeting [22–24]. Studies on these mice have contributed a lot to understanding the role of this receptor in the biological activities of TNF. It is clear that TNF has a key role in immunity and immunomodulation as well as pro-inflammatory and antitumor activities. Resistance against bacterial infection, e.g. *Listeria monocytogenes*, is mediated by TNFR1: mice deficient in TNFR1 are extremely sensitive to *L. monocytogenes* and other Gram-positive bacteria, including *Yersinia enterocolitica* [25,26], *Pseudomonas aeruginosa* [27], *Legionella pneumophila* [28] and *Burkholderia pseudomallei* [29], and also to other pathogens, such as viruses, e.g. influenza virus [30] and vaccinia virus [31]. However, injection of TNF in mice leads to systemic inflammation, which, depending on the dose, can be lethal. Studies on TNFR1 knockout (KO) mice have shown that lethality, which involves inflammation [32] and necroptosis [19], is mediated entirely by TNFR1. Chronically overexpressed TNF leads to arthritis and inflammatory bowel diseases, both of which depend on TNFR1 [33]. TNF-induced antitumor effects are also mediated entirely by TNFR1 on host-derived neo-vascular endothelial cells, which grow into the tumor and are important for sustaining tumor growth and survival [34].

Anti-TNF therapy is effective for treatment of autoimmune diseases such as rheumatoid arthritis and inflammatory bowel diseases, indicating that the TNF signaling pathway is an appropriate target [35,36]. Nevertheless, long-term TNF blockade

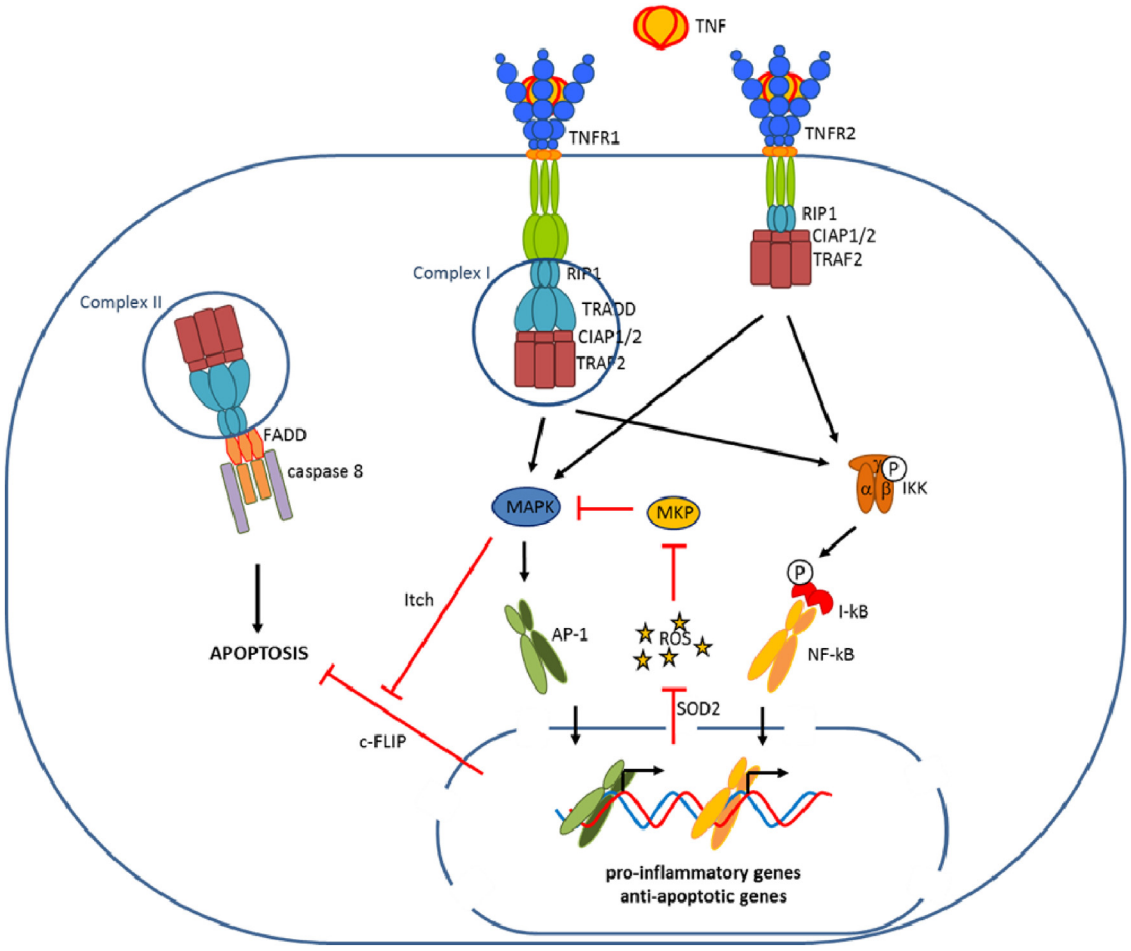

Fig. 3. TNFR1 pathway. Binding of TNF to TNFR1 triggers recruitment of TRADD, TRAF2, CIAP1/2 and RIP1, forming complex I. Activation of the IKK complex, leads to proteolytic degradation of I-κB proteins and subsequent activation of NF-κB which is then translocated to the nucleus to activate transcription of target genes. Upon endocytosis of complex I, TRADD dissociates from TNFR1 and associates with FADD and caspase 8 to form intracellular complex II. Caspase 8 becomes activated and initiates apoptosis. For detailed description, see text.

can cause substantial side-effects, such as opportunistic infections [37] and development of additional autoimmune diseases, including lupus, type 1 diabetes, uveitis, multiple sclerosis and psoriasis, as well as lymphoma and leukemia [38,39].

Interestingly, TNFR1 +/− mice, which express 50% TNFR1 on cells, were also found to be completely resistant to TNF-induced lethal inflammation over a huge dose range [40]. These data, together with others, such as those showing that mice expressing higher levels of cell-bound TNFR1 develop spontaneous inflammation [41], suggest that TNFR1 is a potential drug target, and that minor TNFR1 regulation might have substantial physiological and pathological effects. Furthermore, in humans, mutations affecting TNFR1 have been linked with the development of TNFR1-associated periodic syndromes (TRAPS), which are characterized by recurrent fever attacks and localized inflammation [42]. Hence, selective inhibition of TNFR1 signaling might be a better alternative for the treatment of TNF/TNFR1-mediated autoimmune diseases because it would reduce the pro-inflammatory actions of TNFR1 without impairing the immunosuppressive properties of TNFR2 [43,44]. A variety of compounds have already been generated, including monoclonal antibodies and derivatives, antagonistic TNF variants (R1AntTNF), RNAi and antisense oligo's (ASOs), which are all able to inhibit TNF-mediated NF-κB gene expression and apoptosis. Many of these inhibitors have already proven to block TNF-induced lethality, allowing safe anti-tumor therapy [40,45], while others have shown to be protective in mouse models of several TNF-induced chronic disease, such as CIA, EAE, RA, VILI, CCL4-, conA- and TNF/GalN-hepatitis [46–53].

TNF receptors form homotrimers upon activation by TNF but no heterotrimers are assembled and the TNFR1/TNFR2 protein ratio has been found to be important for the TNF response. TNF affects NF-κB activation predominantly through TNFR1, whereas TNFR2 activates transcription poorly [54]. Nevertheless, TNFR2 stimulation can result in competition for TRAF2 and cIAPs and thereby inhibit TNFR1-induced NF-κB transcription. Reduction of NF-κB activation promotes apoptosis in certain cell types due to diminished production of anti-apoptotic factors [55]. Hence, constant TNFR1 expression coupled to changeable TNFR2 levels alters the TNFR1/TNFR2 ratio and controls the response of the cell to TNF stimulation [56]. On the other hand, the kinetics of TNF binding to TNFR2 suggests a mechanism by which TNFR2 might increase the apparent rate of TNF binding to TNFR1. TNFR2 has a higher affinity and longer TNF-binding half-life than TNFR1. By a so-called ligand-passing mechanism TNFR2 is thought to associate with TNF, increasing its concentration near TNFR1 receptors, and making TNF available for activating TNFR1 [57]. Clearly, the outcome of TNFR1 and TNFR2 signaling is complex and may also depend on the cell type and the activation status of the cell.

As an important step to completely understand the biology of TNF and its receptors and to develop specific TNFR1 inhibiting

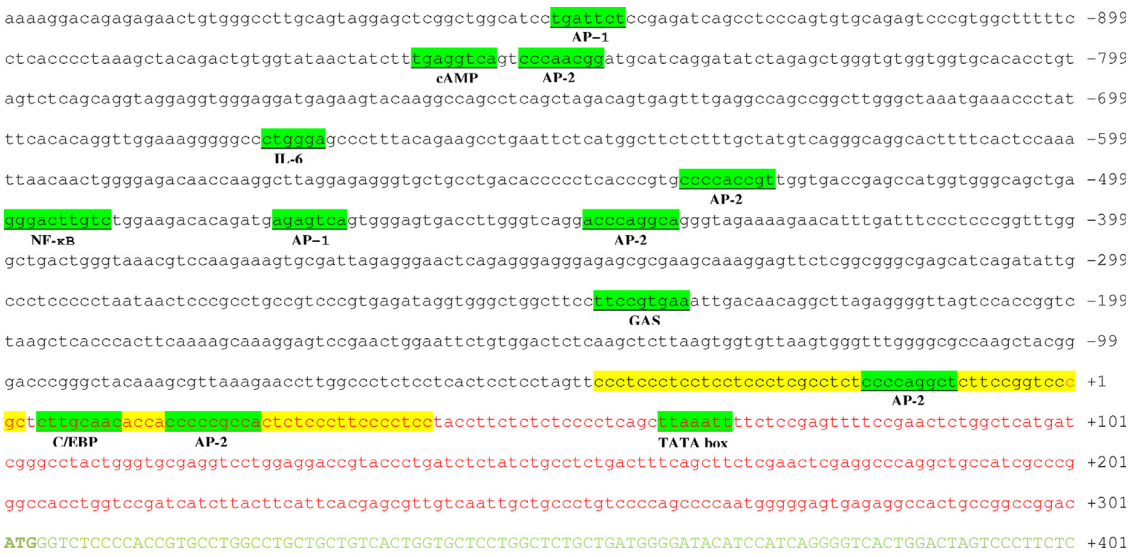

Fig. 4. Promoter of mouse Tnfrsf1a (NM011609). The 5′UTR is shown in red and the CDS in green. Transcriptional regulatory sequences are marked in green and the GC rich elements in yellow.

tools, a comprehensive overview of the available knowledge about regulation of TNFR1 on all levels is provided in this review.

3. Transcriptional and posttranscriptional regulation of TNFR1

3.1. Transcriptional regulation of TNFR1 expression

Despite the critical role that TNFR1 plays in TNF-mediated signaling, little is known about the regulation of its promoter. It has been suggested that the TNFR1 promoter is constitutively active, like the promoters of "housekeeping" genes, at low levels and in all nucleated cell types [56,58]. TNFR2, on the other hand, is inducible and expressed exclusively by immune cells, endothelial cells and some neuronal populations [59].

3.1.1. Promoter analysis

The 5′ flanking region of the TNFR1-coding gene (*TNFRSF1A* in humans and *Tnfrsf1a* in mice) was scanned for the presence of sequence motifs that have been associated with regulation of gene transcription [60]. According to the UCSC genome browser, the transcription start site (TSS) is located 107 bp upstream of the putative TSS that was described by Takao and Jacob. A putative **TATA box** (TTAAATT), the core promoter sequence, is now located between +63 and +69 downstream of the TSS, which presumes that it may not be a true TATA box. Two **GC-rich elements** are present between −44 and +3 and between +5 and +42. These elements have been shown to possess enhancer activity in many eukaryotic genes [60].

The TNFR1 promoter contains a functionally important **binding site** for CCAAT/enhancer binding protein **(C/EBP)**, which contributes to the constitutive activity of the promoter. C/EBP transcription factors play essential roles in regulating different cellular processes, including differentiation, energy metabolism, and inflammation. Both C/EBPα and C/EBPβ bind to a sequence located between +5 and +12 [60,61]. There are two copies of the consensus **binding site for AP-1**, a transcription factor that regulates gene expression in response to different stimuli, including cytokines, growth factors, stress, and bacterial and viral infections [60]. Also four potential binding sites for the **AP-2** family of transcription factors (AP-2α, AP-2β, AP-2γ, AP-2δ and AP-2ε) have been found. The general functions of this family are stimulation of proliferation and suppression of differentiation during embryonic development [62]. An **NF-κB binding site** in the promoter between −489 and −498 activates the expression of TNFR1. This element is active and important, since in mammary-specific β-lactoglobulin $Cre^{+}/Ikk2^{fl/fl}$ mice, NF-κB DNA-binding activity is diminished by 50%, leading to reduced expression of TNFR1 mRNA levels and reduction of TNF-induced apoptosis [63]. A consensus sequence related to the **IFNγ activated site (GAS)** of signal transducer and activator of transcription (**STAT-1**) factors has been found between −235 and −243 of the mouse TNFR1 promoter. In oligodendrocytes, IFNγ indeed induces TNFR1 transcription via activation and binding of STAT-1 homodimers to the GAS site in the TNFR1 promoter [64,65] (Fig. 4 and Table 1).

3.1.2. Factors affecting TNFR1 expression

Gene transcription is controlled by dynamic acetylation and deacetylation of histone proteins (and other proteins), which alter chromatin structure and affect transcription factor access to the DNA.

HDAC5 (histone deacetylase 5) overexpression has been shown to inhibit tumor cell growth and induce spontaneous apoptosis by altering gene expression, including a fourfold up-regulation of TNFR1 [66]. Transcriptional up-regulation of TNFR1 by **NF-κB** activation has been observed and been shown to influence the contact between T-cells and monocytes [67]. Moreover, **IL18** and

Table 1
Transcriptional regulatory sequences in the promoter of *Tnfrsf1a*. Lower case indicates deviations from the consensus (Y = C/T, R = A/G, M = A/C, K = G/T, W = A/T, S = G/C).

Transcriptional element	Consensus sequence	Actual sequence	Position
TATA box?	TATAWAW	TtaAAtT	+63/+69
C/EBP binding site	RTTGCGYAAY	cTTGCaac	+5/+12
GC rich element			−44/+3
			+5/+41
AP-1 binding site	TGASTCA	TGAtTCt	−941/−947
		aGAGTCA	−467/−473
AP-2 binding site	GCCNNNGGC	cCCAACGGa	−843/−850
		cCCCACcGt	−527/−535
		aCCCAGGca	−436/−444
		cCCCAGGct	−11/−19
		cCCCCGcca	+17/+25
NF-κB binding site	GGGACTTTCC	GGGACTTgtC	−489/−498
IL-6 responsive element	CTGGGA	CTGGGA	−669/−674
cAMP responsive element	TGACGTCA	TGAgGTCA	−853/−860
IFNγ activated site	TTCNNNGAA	TTCCGTGAA	−235/−243

IL18Rα up-regulate the expression of both TNFR1 and TNFR2 on the surface of monocytes by activating the NF-κB pathway. A neutralizing mAb to T-cell membrane-bound TNF decreased the enhancement of TNF and IL1β production by IL18 on cell contact, suggesting that IL18 up-regulates TNF receptor expression and thereby stimulates cross-talk between monocytes and activated T-cells [68]. Also **Vitamin D3** enhances TNF-induced NF-κB activation and TNF-induced apoptosis in MCF-7 cells. This effect could be explained by an up-regulation of surface expression of TNFR1. The Vitamin D effect, however, changes the balance between death-inhibiting and death-promoting signals in favor of increased apoptosis [69]. On the other hand, **IL3 and GM-CSF** can down-regulate both mRNA and surface expression of TNFR1 and TNFR2. This leads to inhibition of TNF-induced differentiation of osteoclasts from hematopoietic precursors of the monocyte lineage [70]. **IL10** also causes a down-regulation of membrane TNFR1 and TNFR2 on monocytes and reduces the pro-inflammatory potential of TNF in three ways: by down-regulating membrane TNF receptor expression, by increasing the production of soluble TNF receptor, and by inhibiting TNF release. The data suggest that IL-10 may be useful in the treatment of diseases involving over-expression of TNF and that part of the effect is due to TNFR1 downregulation [71]. Finally, over-expression of **STAT3** completely inhibited IL10-induced suppression of TNF receptor expression [72].

3.1.3. Transcription factor prediction

The interaction of transcription factors with transcription factor binding sites (TFBSs) is the primary mechanism in the regulation of transcription. Since TFBSs are short DNA sites of 6–15 bp, *in silico* predictions simply based on their primary sequence are only partly reliable. We searched for TFs that can target *Tnfrsf1a* in both mouse and human by using a new online TFBS prediction program called PhysBinder. In addition to sequence data, this program makes use of biophysical properties of protein–DNA complexes such as the flexibility of the DNA [73]. In our *in silico* TFBS predictions, we further took into account the conservation among vertebrates, DNase hypersensitivity that predicts open chromatin clusters and markers that are found near regulatory elements (H3K4Me1) and promoters (H3K4Me3) based on ENCODE data using the UCSC human genome browser. Applying a stringent threshold, we found seven TFBSs specific for human *TNFRSF1A*, five TFBSs specific for mouse *Tnfrsf1a* and 25 TFBSs that are common to the mouse and human gene (Table 2).

The complete results for the human *TNFRSF1A* can be consulted using the following link (http://genome.ucsc.edu/cgi-bin/hgTracks?hgS_doOtherUser=submit&hgS_otherUserName=lpuimege&hgS_otherUserSessionName=hg19_TNFRSF1A_review%20Physbinder) and the mouse results can be found on (http://genome.ucsc.edu/cgi-bin/hgTracks?hgS_doOtherUser=submit&hgS_otherUserName=lpuimege&hgS_otherUserSessionName=mm9_TNFRSF1A_review).

3.2. Post-transcriptional regulation of TNFR1 expression

A key aspect of the regulation of eukaryotic gene expression is cytoplasmic control of mRNA stability, translation and degradation [74]. Regulation at the translational level can provide a quick response to stimuli because it does not involve the process of gene expression. Furthermore, translational regulation is usually reversible, as it is often mediated through reversible protein modifications such as the phosphorylation of translation initiation factors.

3.2.1. RNA binding proteins

It has been shown that phorbol esters such as TPA lead to a complete loss of TNFR1 at the cell surface of human monocytes, a phenomenon related to decreased stability of TNFR1 mRNA and associated with changes in the formation of RNA–protein complexes. This decrease is partial and thus appears to be only one of several mechanisms that lead to the complete loss of TNFR1 from the surface of those cells [38]. TPA activates protein kinase C and can modulate gene expression by affecting transcription, but it also affects gene regulation by altering the stability of mRNAs. In monocytes, TPA changed the relative amounts of TNFR1 mRNA bound proteins. The nucleotide sequences involved in the formation of the RNA–protein complexes were found to be located in exon 2 of the TNFR1 mRNA. Unfortunately, the identities of the proteins are not yet known. TNFR1 mRNA does not contain RNA destabilizing AU rich elements (AREs), which are found in 3′ UTRs of many cytokine genes, e.g. in the TNF-coding gene [75,76].

3.2.2. microRNAs

Over the past decade, microRNAs (miRNAs) have emerged as important regulators of translation and mRNA stability. MiRNAs can down-regulate gene expression by two post-transcriptional mechanisms, mRNA cleavage or translational repression, depending on the target. When a miRNA guides cleavage, the cut is at precisely the same site as in siRNA-guided cleavage, i.e. between the nucleotides pairing to residues 10 and 11 of the miRNA. After cleavage of the mRNA, the miRNA remains intact and can recognize and cleave other mRNA copies [77].

Hundreds of microRNA molecules and their possible targets have been discovered in the genomes of plants and animals [78]. Strikingly, bioinformatics analyses suggest that up to 30% of human genes might be regulated by miRNAs [79]. We searched for miRNAs that can target *Tnfrsf1a* by using the following miRNA target prediction programs: MicroCosm, miRanda, miRGen, NBmiRTar, TargetScan, miRDB, DIANAmicroT, microInspector, miRWalk, PicTar, PITA, RNA22 and RNAhybrid. By using several programs based on algorithms focusing on different features such as (seed) complementarity, conservation and thermodynamics, we made a comparative analysis (Table 3).

3.3. Post-translational regulation of TNFR1 expression

3.3.1. Storage

After translation in the endoplasmic reticulum, TNFR1 is localized predominantly in the **Golgi apparatus**. The intracellular death domain is required for retention of TNFR1 in the Golgi apparatus: deletion of the entire TNFR1 intracellular domain or the C-terminal DD allowed expression of the receptor on the plasma membrane [80]. Deletions in the cytoplasmic tail demonstrated that a C-terminal sequence of 23 amino acids is required for targeting to the *trans*-Golgi network. This sequence is partly outside the death domain and contains an acidic cluster. Interaction of this sequence with membrane traffic adaptor

Table 2
TF binding site prediction for *Tnfrsf1a*. 1/green indicates predicted, 0/red indicates not predicted.

	MAFK	SP4	SREBF1	STAT1	RAD21	ELK4	Mycn	EGR1	REST	SP2	USF2	NANOG	CTCF	ELK1	ETS1	FOS	GABPA	GATA1	GATA2	KLF4	MAFF	MEF2C	RELA	SPI1	RUNX3	STAT3	TEAD4	ZEB1	BACH1	ELF1	ESSRA	IRF3	JUNB	GTF3C2	Essrb	Tfcp2l1	Zfx
hg19_human *TNFRSF1A*	1	1	1	1	1	1	1	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
mm9_mouse *Tnfrsf1a*	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Table 3
miRNA target prediction for Tnfrsf1a. 1/green indicates predicted, 0/red indicates not predicted.

	microCosm	miRanda	miRGen	NBmiRTar	TargetScan	miRDB	DIANA-microT	microInspector	miRWalk	PICTAR	PITA	RNA22	RNAhybrid	sum
mmu-mir-29a/b1	1	1	1	0	1	0	1	0	1	1	1	0	0	8
mmu-mir-29b2/c	1	1	1	0	1	0	1	0	1	1	1	0	0	8
mmu-mir-125a	1	0	1	1	1	0	1	1	1	0	1	0	0	8
mmu-mir-680-1	1	1	1	0	1	0	1	1	1	0	1	0	0	8
mmu-mir-351	1	0	1	0	1	0	1	1	1	0	1	0	0	7
mmu-mir-763	1	1	1	0	1	0	1	0	1	0	1	0	0	7
mmu-mir-125b	1	0	1	0	1	0	1	0	1	0	1	0	0	6
mmu-mir-149	0	0	1	0	1	0	1	1	1	0	1	0	0	6
mmu-mir-511	1	1	0	0	1	0	0	1	1	0	1	0	0	6

proteins may play an important role in controlling the cell's response to TNF [81]. The Golgi pool of TNFR1 is believed to serve to replenish cell surface TNFR1 receptors (Fig. 5).

3.3.2. Shedding

TNFR1 can be released from the cell surface by a proteolytic process called ectodomain shedding (Fig. 5). Like TNF, TNFR1 and TNFR2 are cleaved by TNF-α converting enzyme (TACE) [1]. Proteolytic cleavage of TNFR1 decreases the surface expression. Moreover, the generation of antagonistic soluble receptors by shedding can regulate TNF bioactivity by preventing its binding to membrane receptors [82]. TACE may therefore exert either pro- or anti-inflammatory effects, depending on whether it acts on an effector cell (e.g. releasing TNF from macrophages) or target cell (e.g. releasing TNFR1 from endothelial cell) [83]. However, low levels of sTNFR may stabilize the activity of TNF and provide a reservoir of TNF [84]. In humans, mutations affecting the shedding of TNFR1 have been linked with the development of TNFR1-associated periodic syndromes (TRAPS), which are characterized by recurrent fever attacks and localized inflammation. Similarly, knock-in mice expressing a mutant non-sheddable TNFR1 are very sensitive to TNF-induced inflammation and develop several

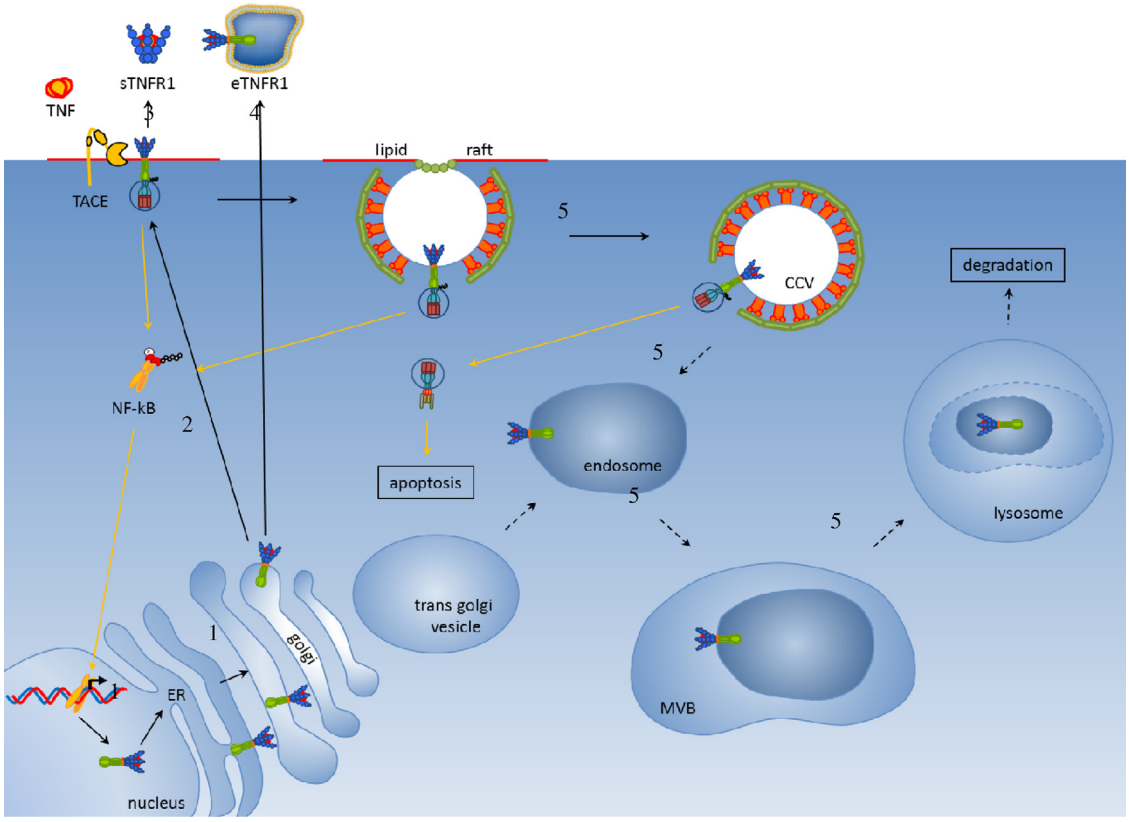

Fig. 5. Compartmentalization of TNFR1 signaling. Black arrows indicate transport of TNFR1, 1 = translation and storage, 2 = membrane expression, 3 = shedding, 4 = exocytosis, 5 = endocytosis. Yellow arrows indicate signaling pathways. For detailed description, see text.

auto-immune-like diseases, such as spontaneous hepatitis, arthritis, and autoimmune encephalomyelitis [41].

Basal expression of TACE is observed in all vasculature cell types, including endothelial cells, vascular smooth muscle cells, fibroblasts, and leukocytes. TACE-mediated shedding is enhanced by stimulation with pro-inflammatory cytokines (TNF, IFNγ), TLR ligands (LPS), growth factors (PDGF, VEGF), GPCR ligands (thrombin) or oxidative stress (ROS), and thus involved in many regulatory pathways. Transcriptional regulation, maturation by furin, trafficking from storage pools, intracellular phosphorylation, changes in cellular distribution within membrane lipid rafts, interaction with adapter molecules (tetraspanins) and conformational changes of the protease all lead to enhanced substrate cleavage by TACE [85]. TACE is expressed in intracellular compartments and on the cell surface. Removal of its pro-domain by a furin protease probably occurs within the Golgi apparatus [86]. Distribution of TACE and its substrates within lipid rafts affects shedding because mature TACE is associated with cholesterol-rich lipid rafts, and depletion of rafts induces shedding of TNF, TNFR1 and TNFR2 [87,88]. MAP kinases, oxidative stress and other TACE regulating pathways have been studied in great detail [89–93].

The mechanism of TNFR1 shedding might also involve interactions with regulatory ectoproteins. A direct relationship exists between the level of the type II integral membrane protein **ARTS-1** (aminopeptidase regulator of TNFR1 shedding) and the degree of TNFR1 shedding. ARTS-1 overexpression increases TNFR1 shedding and decreases membrane-associated TNFR1, while expression of antisense ARTS-1 mRNA decreases membrane-associated ARTS-1 and TNFR1 shedding but increases membrane-associated TNFR1. ARTS-1 neither bound to TNFR2 nor altered its shedding, indicating its specificity for TNFR1. Findings suggest that ARTS-1 does not possess TNFR1 sheddase activity, which indicates that it is a multifunctional ectoprotein capable of binding to and promoting TNFR1 shedding [94].

3.3.3. Exocytosis

TNFR1 shedding is a consequence of proteolytic cleavage of the 28-kDa ectodomain by TACE. But in human vascular epithelial cells (HUVECs) and bronchoalveolar lavage (BAL) fluid, the predominant form of soluble TNFR1 is the full-length 55-kDa protein (eTNFR1) associated with **exosome-like vesicles** (Fig. 5). Exosomes are small membrane-enclosed vesicles of 30–100 nm released from the cell by exocytosis. These intracellular TNFR1-containing vesicles enable constitutive release of full length TNFR1 into the extracellular compartment. This is an alternative pathway for generating soluble cytokine receptors independently of proteolytic cleavage of the receptor ectodomain [95]. It has been reported that histamine induces redistribution of TNFR1 from the Golgi to vesicles and subsequently into the medium as soluble receptors, with a consequent decrease in cell surface TNFR1 [82]. The precise significance of such remarkable full-length TNFR1 shedding is still unclear.

3.3.4. Ligand-binding and lipid rafts

Upon binding of TNF, TNFR1 translocates to cholesterol- and sphingolipid-enriched membrane microdomains called **lipid rafts**, where the associations with RIP1 and the adaptor proteins TRADD and TRAF2 occur and form the signaling complex I (Fig. 3). This complex triggers pathways leading to induction of pro-inflammatory and anti-apoptotic proteins. Activation of p42, a member of the MAP kinase family, leads to TNFR1 phosphorylation at a consensus MAPK site in the cytoplasmic domain, which alters its subcellular localization, resulting in changes in its signaling properties [96]. Moreover, in lipid rafts TNFR1 and RIP1 become ubiquitinated, which leads to their degradation via the proteasome pathway [97]. Disruption of lipid rafts, by depleting cholesterol, not only abolishes ubiquitination but also totally blocks TNF-induced NF-κB activation, leading to a switch to apoptosis induction which indicates that the translocation of NF-κB to lipid rafts is essential for its activation [98]. So, the subcellular localization of TNFR1 determines its available amount and signaling outcome.

3.3.5. Endocytosis

Formation of complex I is transient because most of TRADD, RIP1 and TRAF2 dissociate from TNFR1 within an hour, when TNFR1 starts to undergo endocytosis (Fig. 5). Treatment of cells with TNF led to maximal down-modulation of the TNF receptors within 30 min. Ligand-induced down-modulation of TNF receptors is caused by TNFR1 internalization [99]. The liberated DD of TRADD now binds to FADD, resulting in caspase 8 recruitment and complex II formation. Complex II initiates apoptosis, provided that NF-κB signaling has terminated [98]. Endocytosis or TNFR1 internalization and intracellular trafficking plays an important role in selection of the signaling pathway: either internalization-independent (pro-inflammatory complex I) or internalization-dependent (pro-apoptotic complex II). Apoptosis is totally blocked by preventing internalization with monodansylcadaverine (MDC), an inhibitor of transglutaminase, a membrane-bound enzyme that actively participates in internalization of various receptor systems [100]. The endosome should therefore be recognized as a signaling organelle involved in selectively transmitting death signals from TNFR1 [101]. Internalization proceeds through the classical receptor-mediated endocytosis pathway, i.e. via clathrin-coated vesicles and endosomes that fuse and enter multivesicular bodies (MVB) before accumulating in lysosomes [102]. After apoptosis, TNFR1 protein can be eliminated in a caspase-dependent manner. *In vitro*, the cytoplasmic tail of hTNFR1 is susceptible to cleavage by the downstream executioner caspase 7, the only caspase capable of cleaving TNFR1. Identification of the cleavage site revealed an EXE motif instead of the classic EXD motif. Homologous sequence alignments showed that the EXE motif is conserved in rat and pig but not in mouse and cow, which have 3–4 missing amino acids at this site [103]. TNF thus causes the down-modulation of its own receptor by internalization which might function as a negative feedback mechanism as it will desensitize cells for further TNF stimulation until the membrane TNFR levels have recovered.

4. Dysregulation of TNFR1 expression

4.1. TNFR1 genetic variants

4.1.1. Missense mutations

TNF receptor-associated periodic syndrome (**TRAPS**) is caused by missense mutations in the TNFRSF1A gene and characterized by periodic high fevers, rashes, abdominal pain, chest pain, conjunctivitis, arthralgia and myalgia. More than 100 mutations have been identified in TNFR1, all of them in the extracellular domain. (http://fmf.igh.cnrs.fr/ISSAID/infevers) [104]. TRAPS mutations occur predominantly in CRD1 and CRD2 and many of them involve intramolecular disulfide bonds. Others occur at residues predicted to have an effect on the secondary structure or at residues involved in hydrogen bonds between loops of the receptor. The absence of large deletions suggests that synthesis of the mutant protein is important for pathogenesis. It has been hypothesized that TRAPS pathology is driven by defective receptor shedding resulting in reduced serum levels of soluble TNFR1. This hypothesis was based on observations that cells of some TRAPS patient are resistant to PMA-induced shedding and that serum from TRAPS patients contained reduced levels of

circulating TNFR1. However, the shedding defect was not always present and varied depending on the studied cell types [105]. Molecular modeling indicates that nine TNFR1 mutants are unable to bind TNF (H22Y, C30S, C30R, C33G, C34S, T50M, C52F, C88R, R92P), whereas the R92Q and P46L mutants can bind TNF. Due to misfolding, they accumulate in the endoplasmic reticulum (ER) instead of localizing to the cell surface, and are most likely degraded by the proteasome [106]. But accumulation of mutant TNFR1 in the ER may also trigger the ER stress response, which can directly or indirectly lead to inflammation or to reduced TNF-induced apoptosis. Interestingly, neutrophils and dermal fibroblasts from TRAPS patients with several different mutations have reduced apoptosis but produce the proinflammatory cytokines IL-6 and IL-8 normally when exposed to TNF [107,108]. Failure of activated cells to undergo apoptosis in TRAPS could lead to accumulation of pro-inflammatory cytokines. However, TRAPS mutations might not all act by the same mechanism [109,110]. Glucocorticoids are effective in decreasing the severity and duration of the fever attacks, although their efficacy fades with time [111]. The soluble TNF receptor Etanercept, the IL-1β receptor antagonist Anakinra and the IL-6 receptor antagonist Tocilizumab are effective in some patients. However, since no controlled clinical trials have been performed for this rare syndrome, there is currently no single recommended treatment [112].

Two rare single amino acid mutations in *TNFRSF1A* have been identified as low-penetrance risk factors for TRAPS. The R92Q substitution is carried by ~2% of North American and Irish populations, and the P46L mutation is present in 9% of African populations. TRAPS patients with these polymorphisms have a milder syndrome with almost no incidence of amyloidosis [42]. But the R92Q mutation has also been linked with other diseases associated with inflammation, such as **rheumatoid arthritis** and **atherosclerosis** [113,114]. Clinical observations have identified some **multiple sclerosis** (MS) patients carrying the R92Q mutation and exhibiting additional TRAPS symptoms. The co-existence of MS and TRAPS could be mediated by this mutation. The R92Q mutation acts like a genetic risk factor for MS and other inflammatory diseases, including TRAPS. Nevertheless, this mutation does not appear to be a severity marker, modifying neither the progression of MS nor its response to therapy. But an alteration in TNF/TNFR1 signaling may increase pro-inflammatory signals [115].

Single nucleotide polymorphisms (SNPs) in the *TNFRSF1A* gene may also influence the innate immune response against **invasive pulmonary aspergillosis** (IPA), an increasingly common opportunistic fungal infection that usually occurs in immune compromised patients [116]. In this infection, TNF acting through TNFR1 plays a pivotal role in immune regulation and host immune responses. Three SNPs were genotyped in 275 individuals (52% immunocompromised hematological patients with high-risk of developing IPA and 48% healthy controls): A383C and G609T in the 5′ UTR, and A36G in exon 1. The last two are associated with IPA susceptibility. The role of *TNFRSF1A* SNPs is also supported by significantly lower TNFR1 mRNA levels in IPA compared to IPA-resistant patients and by a strong correlation between the −609 SNP and TNFR1 expression levels. TNFR1 polymorphisms may influence the risk of IPA disease and might be useful for risk analysis [117]. The A36G mutation is also significantly associated with lower hemoglobin levels, causing iron deficiency anemia in patients with early or established rheumatoid arthritis. The frequency of anemia is higher in GG homozygous patients [118,119].

The pathologies induced by mutations in TNFR1 further emphasize the important role of TNFR1 in autoimmune diseases and immunity. Furthermore, they indicate that TNFR1 targeting might be a better alternative to current TNF inhibition therapies since Etanercept and Infliximab fail in certain TRAPS family with T50M, C30S and R92Q mutations [120,121].

4.1.2. Alternative splicing

Two disease-associated isoforms of TNFR1 mRNA produced by alternative splicing were recently described.

The **TNFR1-Δ6** splicing pattern is caused by a variation (rs1800693) in the exon 6/intron 6 border region that alters exon 6 splicing. The frame shift caused by skipping of exon 6 results in a protein lacking the intracellular and transmembrane domains and part of the extracellular domain. This TNFR1 splice form is associated with multiple sclerosis (MS) but not with other autoimmune conditions such as rheumatoid arthritis, psoriasis or Crohn's disease. The MS risk allele induces the expression of a soluble TNFR1 form that can block TNF. Importantly, TNF-blocking drugs can promote onset or exacerbation of MS, but they are very effective for autoimmune diseases that are not associated with rs1800693. This indicates that the clinical experience with these drugs corroborates the disease association of rs1800693, and that the MS-associated TNFR1 variant mimics the effect of TNF-blocking drugs [122].

The **TNFR1-Δ2** splice variant is regulated by three variations affecting the phenotype of TRAPS. They occur in the promoter, exon 1 and intron 4 (rs4149570, rs767455 and rs1800692, respectively) of the *TNFRSF1A* gene. Exon 2 alternative splicing increased with the T-A-T haplotype at rs4149570–rs767455–rs1800692 as compared with the G-G-C haplotype and transcriptional activity increased with the T-T haplotype compared with the G-C haplotype, suggesting that regulation of TNFR1-Δ2 expression may occur via a coupling mechanism between transcription and splicing. Whereas TNFR1 is ubiquitously expressed, TNFR1-Δ2 is expressed tissue-specifically in human PBLs, brain, heart, kidney, skeletal muscle, small intestine and spinal cord, but not in liver or lung [123].

4.2. TNFR1 in human diseases

Because TNF is a key immune system modulator and has broad effects, excessive signaling can cause significant damage. A delicate balance exists between beneficial immune stimulation and pathogenesis. Several autoimmune and inflammatory diseases have been associated with the effects of dysregulated TNF activation [7]. It is not always evident whether abnormal levels of TNF, TNFR1 or signaling components are the cause or consequence of a given pathology. Therefore, understanding the regulation of TNF and its receptors is essential for elucidating how TNF can either prevent or induce various diseases. Here (Table 4), we provide an overview of misregulations in TNF/TNFR levels as described in several human diseases.

Patients with **systemic lupus erythematosus** (SLE), a multi-organ inflammatory autoimmune disease, have altered expression of TNF-related signaling molecules, suggesting that imbalance of TNF signaling favors cellular activation rather than apoptosis. SLE patients have increased levels of TNFR1, TNFR2 and TRAF2 and decreased levels of RIP1 on various naive and memory B-cell and T-cell subsets as compared to controls. However, the levels of these molecules are not correlated with their RNA expression or with serum TNF levels in peripheral whole blood [124] (Table 4).

Up-regulation of the intercellular adhesion molecule (ICAM)-1 on human conjunctival epithelial cells (HCECs) is an important feature of **ocular allergic inflammation**. TNF produced by human conjunctival mast cells up-regulates the expression of TNFR1 on HCECs, resulting in a stronger TNF-mediated response, including up-regulation of ICAM-1. So, up-regulation of TNFR1 expression results in enhanced ICAM-1 expression in response to TNF

Table 4
The regulation of TNFR1 in several TNFR1-mediated diseases. For detailed description, see text.

Disease	Biomarker	Tissue	Effect	Ref.
Systemic lupus erythematosus	TNFR1 protein up	B-cells, T-cells	Cellular activation	[124]
Ocular allergic inflammation	TNFR1 protein up	HCECs	I-CAM expression	[125]
Aging	TNFR1 protein up	Lymphocytes	Apoptosis	[126]
Acute myocardial infarct	TNFR1 protein up	Cardiomyocytes, ECs	Angiogenesis down	[127,128]
Ischemic cerebrovascular diseases	sTNFR1 protein up	Serum	Proliferation	[129,130]
Lung epithelium injury	sTNFR1 protein up	BALF	Neutralize TNF	[131]
Lupus nephritis	TNFR1 protein up	Urine	?	[132]
Behcet's disease	sTNFR1 protein up	Serum, synovial fluid	?	[133–136]
Huntington's Disease	TNFR1 mRNA down	Skeletal muscle	?	[137–139]
Hepatocellular carcinoma	sTNFR1 protein up	Serum, ascetic fluid	?	[140,141]
	TNFR1 mRNA down	Liver		[142]

stimulation, demonstrating that targeting TNFR1 expression may be an effective treatment for ocular inflammation [125].

Aging is characterized by increased susceptibility of T-cells to TNF-induced apoptosis due to increased expression of TNFR1 and TRADD and decreased expression of TNFR2 and TRAF-2. Moreover, there is an increased activation of caspase 8 and caspase 3, confirming that increased TNF-induced apoptosis may play a role in T-cell deficiency associated with human aging [126].

Development of arterial diseases is associated with age-related impairment of angiogenesis. Because TNFR1 mediates the cytotoxic effects of TNF, whereas TNFR2 is mostly involved in the protective effects, TNF signaling via its receptors has diverse effects on neovascularization, repair and regeneration in adult tissue after **acute myocardial infarction** (AMI). Intact signaling through both TNFR1 and TNFR2 assures sufficient NF-κB activation, followed by transcriptional activation of *VEGFA*, *FGFB* and other pro-angiogenic genes. But age-associated decrease of TNFR2 levels, coupled with post-ischemic increase in systemic TNF, favors apoptosis in adult cardiomyocytes and endothelial cells due to reduced NF-κB activation, leading to reduced angiogenesis. Decreased TNFR2 expression in adult tissue also stimulates pro-apoptotic signaling through TNFR1 by the release of vacant TRADD [127]. But signaling via both TNFR1 and TNFR2 is necessary to prevent reperfusion injury after AMI during late preconditioning. So, total blocking of TNF is not advised in AMI patients. Modulation of TNFR1 and/or TNFR2 expression at different stages of AMI may have important implications for prevention of myocardial injury and enhancement of myocardial repair and regeneration [128].

Furthermore, it has been shown that patients with **acute ischemic cerebrovascular diseases** also have higher plasma levels of sTNFR1 [129]. Animal studies have shown that TNFR1 is associated with decreased neuronal proliferation after stroke and that deletion of TNFR1 enhances neuroblast formation and recovery. These results provide evidence that TNFR1 is a negative regulator of stroke-induced progenitor proliferation; the proliferative response after stroke might be promoted by blocking TNFR1 signaling [130].

Ozone (O_3) is an air pollutant that causes **lung epithelium injury** leading to inflammation. The inflammatory response to

Table 5
Viral mechanisms of escape from the host response. For detailed description, see text.

Virus	Viral protein	Interference	Mechanism	Ref.
Epstein–Barr virus	BZLF1	TNFR1 transcription	Reduction of TNFR1 promoter activity	[144]
Hepatitis C virus	?	TNFR1 transcription	Inhibition of TNFR1 mRNA expression	
Herpes simplex virus	UL41	TNFR1 translation	Degradation of TNFR1 mRNA and inhibition of apoptosis	[145]
Cytomegalovirus	Immediate early (IE) viral products	TNFR1 Golgi-trafficking	Down-regulation of TNFR1 surface expression	[146,147]
Poliovirus	3A	TNFR1 Golgi-trafficking	Down-regulation of TNFR1 surface expression	[148]
Respiratory syncytial virus	?	TNFR1 shedding	IL10 production and increased production of soluble TNF receptor	[149,150]
Adenovirus	E3-14.7K	TNFR1 internalization	Inhibition of apoptosis and increased NF-κB signaling	[151]
Myxoma virus	Secreted M-T2 (pseudo sTNFR)	TNFR1 signaling	Inhibition of TNF-induced cytotoxicity in T-cells	[152,153]
Myxoma virus	Intracellular M-T2	TNFR1 signaling	Inhibition of apoptosis (T-cells)	[153]
Orthopoxviruses	CrmB,C,D,E (pseudo sTNFR)	TNFR1 signaling	Blocking TNF function	[154]
Epstein–Barr virus	LMP-1 (pseudo TNFR)	TNFR1 signaling	Ligand independent NF-κB activation (infected B-cells)	[155,156]
Human herpes virus 6B	U20	TNFR1 signaling	Inhibition of TNFR1 signaling and apoptosis	[157]
Herpesvirus saimiri	STP (pseudo TNFR)	TNFR1 signaling	Ligand independent NF-κB activation via association with TRAFs (infected T-cells)	[158]
Human papilloma virus 16	E6	TNFR1 signaling	TNFR1 binding with inhibition of TRADD binding and DISC formation leading to reduced TNF-induced apoptosis	[159]
Respiratory syncytial virus	RSV-G protein (pseudo TNFR1)	TNFR1 signaling	Inhibition of TNF-induced apoptosis by I-κB proteolysis	[160]
Hepatitis C virus	HCV core protein	TNFR1 signaling	TNFR1 DD binding with inhibition of TRADD binding, facilitating FADD binding and leading to increased TNF-induced apoptosis (HepG2, Hela)	[161,162]
Hepatitis C virus	HCV core protein	?	Increasing NF-κB nuclear retention and DNA binding and increasing I-κB degradation leading to reduced apoptosis	[163,164]
Hepatitis C virus	HCV core protein	?	Inhibition of TNF-induced apoptosis (MCF7)	
Tanapox virus	Glycopeptide	?	Inhibition of TNF-induced NF-κB activation leading to reduced cell adhesion molecules	[167]
Parvovirus	?	?	Activation of caspase 3 and down-regulation of c-*myc* leading to increased apoptosis	[168,169]

acute ozone exposure includes the production of numerous cytokines and chemokines, resulting in influx of neutrophils. Genetic linkage studies on both mice and humans have shown that a locus encompassing the *TNF* gene plays a role in responses to O_3. In mice, age-related differences in the inflammatory response to acute O_3 exposure vary with TNFR1 expression. In fact, it has been shown that sTNFR1 increases during disease in the BAL fluid, and that this sTNFR1 neutralizes TNF in the lung and so protects against O_3-induced inflammation [131].

Other diseases may also be associated with differences in TNFR1 levels, however the effects are less clear (Table 4). In mice and patients with **lupus nephritis**, an inflammation of the kidney caused by SLE, TNFR1 is found to be enriched in the urine especially at the peak of disease. Whether the increased urinary TNFR1 levels reflect increased shedding and are relevant to disease progression remains unclear [132]. Patients with active **Behcet's disease** (BD), a chronic, multi-organ immunoinflammatory vasculitis that often presents with mucous membrane ulcers, ocular lesions and arthritis, have increased levels of plasma sTNFR1 and sTNFR2, especially when arthritis is present [133]. TNF appears to be important in initiating Behcet's disease, as indicated by the effects of blocking TNF. Infliximab is a promising treatment for uveitis associated with the disease and Etanercept is useful for patients with mainly skin and mucosal symptoms [134–136]. Since the level of TNFR1 correlates well with disease activity index scores of these diseases, the increase may be useful for diagnosis of Behcet's and lupus.

In **Huntington's disease** (HD), a neurodegenerative disorder caused by expansion of a glutamine-encoding CAG repeat which affects muscle coordination and results in cognitive regression and psychiatric problems, the opposite is observed. Mouse models representing the earlier stages of human HD ($Hdh^{CAG(150)}$ knock-in mice) or the later stages of the rare, but more severe, juvenile form of human HD (R6/2 transgenic mice) [137,138] and muscle biopsies from HD patients, showed decreased *Tnfrsf1a* gene expression [139]. Studies with TNFR1 deficient mice could be very useful to confirm these observations.

Hepatocellular carcinoma (HCC) is the fifth most common neoplasia in the world and the first cause of death by cancer in some regions. sTNFR1 levels in the serum and ascites fluid of patients with HCC are significantly higher than in controls, and they correlate positively with total bilirubin and alpha fetoprotein in the peripheral blood. This reflects an abnormal immune status of HCC patients and can help to predict the progression of the tumor [140]. Moreover, the disruption of death receptor-dependent cell signaling is linked to poor survival in patients with HCC [141]. On the other hand, several genetic alterations of the TNF-TNFR superfamily in HCC were detected by sequencing HCC DNA samples. In particular, the TNFR1 promoter −329G/T polymorphism was strongly associated with primary HCC, where the T allele resulted in the repression of TNFR1 expression. Therefore, these results suggest that the TNFR1 329G/T polymorphism may play an important role in the development of HCC [142].

4.3. Viral interference in TNFR1 expression and function

TNF acting via TNFR1 is considered an important anti-viral agent, often acting synergistically with IFNγ [143]. However, growing evidence has shown that both DNA and RNA viruses can interfere with the TNFR1 pathway and thereby escape the host immune response. In infected cells, viral proteins can either affect TNFR1 availability by acting upon transcription, translation, trafficking or shedding of TNFR1, or modulate TNFR1 activity by acting on internalization or signaling of TNFR1 (see Table 5).

Epstein–Barr virus (EBV) immediate-early protein BZLF1 prevents TNF-induced activation of target genes and TNF-induced apoptosis by down-regulation of TNFR1 during the EBV lytic replication cycle. Thus, EBV has developed a mechanism for evading TNF-induced antiviral effects during lytic reactivation or primary infection [144]. The **hepatitis C virus** (HCV) core protein is besides a component of viral nucleocapsids also a multifunctional protein influencing multiple cellular processes. In HCV core protein-activated Hep191 cells, transcriptional profiling identified decreased expression of TNFR1. Since RT-PCR confirmed that TNFR1 is down-regulated and that TNF-induced DNA fragmentation is suppressed in these cells, expression of HCV core protein at physiological levels might inhibit apoptotic cell death of HCV-infected cells [144].

Herpes simplex virus 1 (HSV) uses many strategies to inactivate host functions that are harmful to its replication and dissemination, including taking advantage of the short half-life of TNFR1. Steady-state levels of TNFR1 require continuous renewal by translation of its mRNA, and the HSV viral protein UL41 prevents this constant replenishment by degrading the TNFR1 mRNA [145].

Cytomegalovirus (CMV) is known to target the cell cycle, cellular transcription and immunoregulation to optimize the cellular environment for viral DNA replication. CMV infection also prevents external signaling to the cell by reducing the cell surface expression of TNFR1. Viral early gene products may be responsible for interfering with TNFR1 trafficking through the Golgi apparatus to the cell surface. So, upon infection CMV isolates the cell from host-mediated signals, forcing it to respond only to virus-specific signals [146,147]. **Poliovirus** also triggers host defensive reactions by activating intrinsic (intracellular) and extrinsic (receptor-mediated) apoptotic pathways. Poliovirus nonstructural protein 2A is an inhibitor of cellular translation enhancing the sensitivity to TNFR1-induced apoptosis. On the other hand, poliovirus nonstructural protein 3A neutralizes the pro-apoptotic activity of 2A by eliminating TNFR1 from the cell surface. Consequently, poliovirus infection dramatically decreases TNF receptor abundance on the surfaces of infected cells as early as four hours post-infection. Poliovirus-mediated resistance to TNF is caused by protein 3A interfering with protein trafficking through the endoplasmic reticulum and Golgi: the effect of protein 3A on TNF signaling can be imitated by brefeldin A [148].

Alveolar macrophages and respiratory epithelial cells infected with **respiratory syncytial virus** (RSV) suppress the production of early inflammatory cytokines such as TNF by producing IL10, resulting in an ineffective response to the virus [149]. Moreover, the soluble form of TNFR1, but not TNFR2, was secreted from these cells in a time- and RSV dose-dependent way. As the secretion of soluble TNFR1 blocks TNF responses, increased shedding might be another counteraction against the immune response [150].

The **adenovirus** protein E3-14.7K inhibits TNF-induced apoptosis by preventing TNF-induced TNFR1 internalization, which results in inhibition of the DISC formation. In contrast, E3-14.7K did not affect TNF-induced NF-κB activation via recruitment of RIP-1 and TRAF-2. Inhibition of endocytosis by E3-14.7K is due to a failure in the coordinated temporal and spatial assembly of essential components of the endocytic machinery, such as Rab5 and dynamin2, at the site of the activated TNFR1. This is another mechanism by which Adenoviruses escape the host immune response [151].

Many poxviruses encode several immunomodulatory proteins, such as homologs of host cytokine receptors, also referred to as viroreceptors. These receptors mimic host function by binding to host cytokines, allowing the virus to circumvent the immune defense. The T2 protein of **myxoma virus** (M-T2) is a pseudo TNF receptor that has two distinct activities. The secreted dimeric M-T2 glycoprotein binds TNF with high affinity, inhibiting direct TNF-mediated cytolysis of infected cells and other secondary immune

responses dependent on TNF. However, intracellular M-T2 prevents myxoma-infected T-cells from undergoing apoptosis, supporting viral replication [152,153]. The cytokine response modifier (Crm)-like pseudo TNF receptors, including CrmB, CrmC, CrmD and CrmE and a putative fifth member from cowpox virus that closely resembles CD30, have been identified in several **orthopoxviruses**. These viral TNF receptors resemble secreted versions of the extracellular domains of their counterpart cellular receptors and form functional oligomers that bind and block TNF [154].

The latent membrane protein 1 (LMP1) of **Epstein–Barr virus** (EBV) contributes to the immortalizing activity of EBV in primary human B lymphocytes [155]. LMP1 is targeted to the plasma membrane of infected cells as a constitutive pseudo TNF receptor that activates NF-κB through two independent domains in its cytoplasmic tail. One site is similar to TNFR2 interacting with TRAF1 and TRAF2 and the second site is similar to TNFR1 associating with TRADD. As LMP1 acts independently of the ligand, it replaces the T-cell-derived activation to maintain unlimited B-cell proliferation. LMP1-mediated signaling through the TRAF system plays a role in the pathogenesis of EBV-infected lymphomas that emerge in immunosuppressed patients [156]. Furthermore, the activity of the TNFR1 promoter is dramatically decreased by the EBV protein BZLF1, helping the virus to oppose the anti-viral effects of TNF [144]. Infection by **human herpesvirus 6B** (HHV-6B) blocks caspase 3 and 8 activation and I-κB phosphorylation, indicating inhibition of both the inflammatory and apoptotic signaling pathways. The viral pseudo TNF receptor U20 was shown to localize to the cell membrane, and siRNA knockdown of U20 showed that the protein is necessary for HHV-6B-mediated inhibition of TNFR signaling during infection [157]. The STP pseudo TNF receptors of the **herpesvirus saimiri** (HVS) are stably associated with TRAF1, 2, or 3. Mutational analysis revealed that STP-C488 induces NF-κB activation that correlates with its ability to associate with TRAFs. Thus, TRAF/STP association might be involved in immortalization of T lymphocytes following HVS infection [158]. High-risk strains of **human papillomavirus** (HPV) such as HPV16 cause human cervical carcinoma. The E6 protein of HPV16 mediates the rapid degradation of p53. But transfection of HPV16 E6 into the TNF-sensitive LM cell line protects the cells from TNF-induced apoptosis independently of p53. Caspase 3 and 8 activation is significantly reduced in E6-expressing cells, indicating that E6 acts early in the TNF apoptotic pathway. In fact, E6 binds directly to TNFR1. E6 requires the same TNFR1 C-terminal part for binding as does TRADD, and TNFR1/TRADD interactions are decreased in the presence of E6. HPV E6 binding to TNFR1 interferes with formation of the DISC and thus with transduction of pro-apoptotic signals. HPV, like several other viruses, can evade the TNF-mediated host immune response [159]. Moreover, the central conserved region of the attachment protein G of **respiratory syncytial virus** (RSV) shows structural homology with the fourth subdomain of TNFR1. Although the functions of both protein domains are unknown, the structural similarity of the two protein domains suggests that the cysteine noose of RSV-G may interfere with the antiviral and apoptotic effect mediated by TNF [160].

The **hepatitis C virus** (HCV) core protein binds to the cytoplasmic domain of TNFR1, namely the death domain (DD) thereby inhibiting TRADD binding but facilitating FADD recruitment to TNFR1 [161,162]. By sensitizing cells to TNF-mediated apoptosis, the HCV core protein may provide a selective advantage for HCV replication by enabling evasion of host antiviral defense mechanisms. In contrast, HCV core protein was shown to inhibit TNF-induced apoptosis via NF-κB activation. The expression of the core protein enhances nuclear retention and DNA binding activity of NF-κB and TNF-triggered I-κB degradation. This ability of HCV core protein to inhibit TNF-mediated apoptotic signaling may contribute to the chronically activated, persistent state of HCV-infected cells [163,164]. The controversy among these reports may be attributed to differences in cell types, conditions of core protein expression, and protocols of TNF stimulation [165,166].

Tanapoxvirus (TPV)-infected cells secrete an early 38-kDa glycopeptide that selectively inhibits TNF-induced NF-κB activation and transcriptional activation of cell-adhesion molecules such as E-selectin, ICAM-1 and VCAM-1 on the surface of endothelial cells [167]. **Parvovirus** H-1 infection leads to activation of caspase 3, leading to morphologic changes characteristic of apoptosis and resembling the effects of TNF treatment. This effect is also observed when U937 cells are infected with a recombinant H-1 virus that expresses the nonstructural proteins but in which the capsid genes are replaced by a reporter gene, indicating that the induction of apoptosis can be assigned to the cytotoxic nonstructural proteins in this system. Furthermore, the c-Myc protein, which is over-expressed in the monocytoid cell line U937, is rapidly down-regulated during parvovirus infection, consistent with a possible role of c-Myc in mediating the apoptotic cell death induced by H-1 virus infection. Interestingly several clones derived from the U937 cell line and selected for their resistance to H-1 virus fail to decrease c-Myc expression upon treatment with differentiation agents, and they also resist the induction of cell death after TNF treatment [168,169].

5. Conclusion

TNFR1 mediates the signaling of most cellular effects of TNF. It is involved in numerous physiological and pathological functions at different levels and in different cell types. However, despite extensive knowledge of its signaling pathway, the precise TNF/TNFR1 activation mechanism remains unclear [170]. Moreover, there is still little knowledge about the transcriptional and translational regulation of TNFR1 expression. While the general assumption is that TNFR1 is constitutively expressed and regulated as a housekeeping gene, it is clearly sensitive to many stimuli. Predictions of several transcription factor binding sites and microRNA target sequences suggest that there are many unknown regulators. TNFR1 availability and localization are regulated by diverse mechanisms such as shedding, exosome formation, and internalization. Evidence for the importance of these and other mechanisms of TNFR1 control can be found in the many human diseases that are associated with TNFR1 regulation, levels and activity [42].

Since some of the side effects of the current TNF therapy might be absent with TNFR1 inhibition therapy, further increase of our knowledge on TNFR1 regulation might allow the development of new therapeutic strategies that more effectively target this interesting receptor and the pathogenic TNF signaling.

Conflict of interest

The authors have no conflicting financial interests.

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