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The TL1A/DR3/DcR3 pathway in autoimmune rheumatic diseases

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ABSTRACT

Importance: TNF-like cytokine 1A (TL1A) and its receptors, death receptor 3 (DR3) and decoy receptor 3 (DcR3) are members of the TNF and TNF receptor superfamilies of proteins, respectively. They constitute a cytokine system that actively interferes with the regulation of immune responses and may participate in the pathogenesis of autoimmune diseases.
Objectives: This review aims to present the current knowledge on the role of the TL1A/DR3/DcR3 system in the pathophysiology of autoimmune rheumatic diseases, with a focus on rheumatoid arthritis (RA).
Methods: An extensive literature search was performed in the PubMed database using the following keywords: TL1A, death receptor 3, DR3, decoy receptor 3, DcR3, TNFSF15, TNFRSF25, and TNFSF6B. Studies were assessed and selected in view of their relevance to autoimmune rheumatic diseases.
Conclusion: The TL1A/DR3/DcR3 axis is a novel immune pathway that participates in the pathogenesis of a variety of autoimmune rheumatic diseases. These molecules may be promising therapeutic targets for inflammatory arthritis.

Introduction

The superfamilies of tumor necrosis factor (TNF) ligands and their corresponding receptors (TNFSF and TNFRSF, respectively) consist of several proteins, which are critically involved in the regulation of innate and adaptive immunity [1]. Ligand/receptor binding activates signaling pathways that shape several aspects of the immune response, ranging from apoptosis to autoimmunity. One such TNFSF/TNFRSF system comprises of the TNF-like ligand, TL1A, and its two receptors DR3 and DcR3. The immunological pathways that are mediated by these proteins will be the subject of our review with a focus on their involvement in the pathogenesis of autoimmune rheumatic diseases.

Methods

A systematic literature search was conducted on the PubMed database. We searched for articles published until September 2014, using the following keywords: TNF-like cytokine 1A, TL1A, death receptor 3, DR3, decoy receptor 3, DcR3, TNFSF15, TNFRSF25, TNFSF6B, VEGI, all separately as well as in different combinations. The reference lists of identified articles were searched for further relevant articles. The retrieved articles were assessed according to their applicability to the review subject. Thus, only articles pertaining to the TL1A/DR3/DcR3 axis and its involvement in the subset of autoimmune rheumatic diseases were selected. Studies from animal models and clinical studies were both included. The central findings and main conclusions from this multitude of recent data are summarized in the following parts of the article.

Discovery and characterization of TL1A and its receptors DR3 and DCR3

TNF-like protein 1A (TL1A) was first described in 2002 [2]. In their seminal paper, Migone et al. reported that TL1A is a longer variant of the previously described protein TL1 [alternative name vascular endothelial growth inhibitor (VEGI)]. The gene that encodes for both variants is designated *TNFSF15* in humans (located on chromosome 9q32) and *Tnfsf15* in mice (chromosome 4). TL1A is translated from all four exons of the gene, whereas VEGI is encoded by a continuous DNA sequence spanning from the third to the end of the fourth exon [2]. The C-terminal regions of TL1 and TL1A are identical, whereas no similarity occurs for the N-terminal regions. The produced TL1A protein is a trimeric 28 kDa, type II transmembrane protein, which contains 251 amino acids. Its extracellular part contains the characteristic TNF homology domain [3]. The shorter variant, TL1, lacks a transmembrane region. Like most TNF-like cytokines, the membrane-bound form of TL1A (mTL1A) can be cleaved by enzymes of the matrix

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Table 1
Characteristics of members of the TL1A/DR3/DcR3 system

Molecule	Alternative names	Molecular weight (kDa)	Coding gene	Coding gene location	Soluble form	Membrane-bound form	Cells expressed in
TL1A	TNFSF15	28 (membrane form), 20 (soluble form)	*TNFSF15*	9q32	Yes	Yes	Endothelial cells, monocytes, dendritic cells, macrophages, and T-cell lymphocytes
DR3	Wsl-1, Apo3, LARD, TRAMP, TNFRSF25, and TR3	45	*TNFRSF25*	1p36.3	No	Yes	T-cell lymphocytes, endothelial cells, and osteocytes
DcR3	TR6 and M68	33	*TNFRSF6b*	20q13.3	Yes	No	Tumor cells, T-cell lymphocytes, antigen-presenting cells (monocytes/macrophages, myeloid-derived dendritic cells, and intestinal epithelial cells), synoviocytes, and variety of normal tissue (colon, lung, stomach, spleen, lymph node, pancreas, and spinal cord)

metalloproteinases family and released as a soluble 20-kDa protein (sTL1A), which retains full functionality [3].

TL1A is the only known ligand for death receptor 3 (DR3, designated TNFRSF25) [4]. The first reports of DR3 date from 1996 and a variety of names were assigned to this protein (Wsl-1, Apo3, LARD, TRAMP, TNFRSF25, and TR3) [5–9]. DR3 is a type I membrane protein comprised of 417 amino acids with a molecular weight of 45 kDa and contains a death domain (DD) in its cytoplasmic region [7]. The respective gene was mapped in the human genome at the 1p36.3 position [5–7,9,10]. Both the long (TL1A) and short (TL1) variants of the TNFSF15 products signal through DR3. The effects of ligation by each isoform to DR3-expressing cells have not been tested comparatively. In an isolated exception, Tian et al. reported that VEGI/TL1 (but not TL1A) induced DR3-mediated signals to bone marrow-derived immature dendritic cells, leading to their maturation [11]. Nevertheless, TL1 has been studied for its role in carcinogenesis, almost exclusively, whereas TL1A mostly for its function in the immune system.

DR3 is the member of the TNFRSF with the highest homology to TNFR1 [5]. Nevertheless, in contrast to TNFR1 that is expressed ubiquitously, expression of DR3 appears to be restricted to the lymphocytic compartment. Indeed, abundant expression of DR3 was detected both in tissues enriched for lymphocytes (thymus and spleen) and in peripheral blood lymphocytes [6–8]. In particular, DR3 is expressed on $CD4^+$ and $CD8^+$ cells, as well as natural killer (NK) cells, and is upregulated during activation of the respective populations [5–8,12,13]. Furthermore, although DR3 is not expressed by resting B cells, it is induced by anti-IgM stimulation and becomes detectable on plasma cells [14]. Apart from lymphocytes, there have been reports of DR3 expression in endothelial cells and osteocytes [15,16]. On the other hand, TL1A was first reported to be produced in endothelial cells after stimulation by TNF and IL1β [2]. Subsequent studies detected high TL1A expression in antigen-presenting cells (monocytes, dendritic cells, and macrophages), which is induced via Fcγ-receptor and Toll-like receptor signaling [17–19]. In addition, TL1A may also be expressed by T lymphocytes under inflammatory conditions, via T-cell receptor- or cytokine-mediated stimulation [20]. In general, expression of TL1A by these cells is transient, with the exception of the T cells [20].

In addition to DR3, which is the functional receptor, TL1A may also bind to decoy receptor 3 (DcR3, designated TNFSF6B, also known as TR6 or M68) [21]. DcR3 protein has 300 amino acids, with a molecular size of 33 kDa, and is encoded by the *TNFRSF6b* gene, which is located on chromosome 20 (20q13.3) [22]. DcR3 exists only in soluble form and is detectable in biological fluids [23–25]. There is no murine analog for human DcR3. The main characteristics of the three molecules of the TL1A/DR3/DcR3 system are summarized in Table 1.

Functions of the TL1A/DR3/DcR3 pathway

TL1A/DR3 binding has been associated with two distinct downstream signaling cascades (Fig.). In the first, the adapter protein TNFR-associated death domain protein (TRADD) binds to the cytoplasmic death domain. This, in turn, recruits the TNFR-associated factor (TRAF) proteins, subsequently stimulating mitogen-activated protein kinases (MAPK) and leading to activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [26,27]. The end-point of this process is T-cell co-stimulation. The second cascade differs in that TRADD associates not with TRAF proteins but with Fas-associated death domain (FADD) and caspase 8. This initiating step activates effector

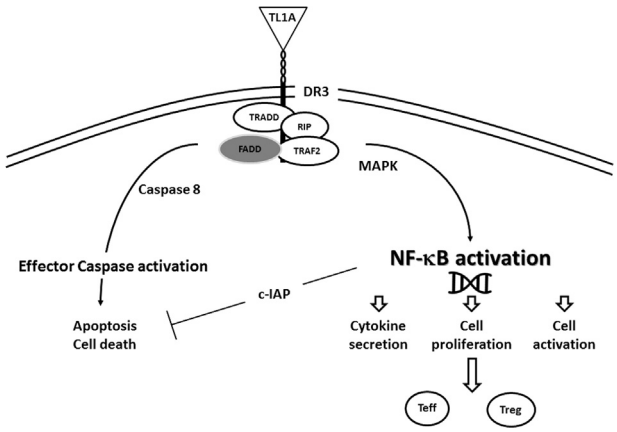

Fig. Ligation of TL1A to DR3 activates two distinct downstream signaling pathways. Both pathways involve binding of adapter protein TNFR-associated death domain protein (TRADD) to the cytoplasmic death domain of DR3. The next step determines the end result of TL1A/DR3 interaction. In the first pathway, the recruitment of the TNFR-associated factor (TRAF) and receptor-interacting (RIP) proteins by TRADD stimulates mitogen-activated protein kinases (MAPK). This in turn induces activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). The final outcome of this process is a pro-inflammatory signal, leading to T cell co-stimulation, with enhancement of T effector via cytokine secretion, cell proliferation, and activation. The function of regulatory T-cell responses is also affected. In the second pathway, TRADD associates with the Fas-associated death domain (FADD) and caspase 8, resulting in the activation of the effector caspases. This pathway will ultimately trigger cell apoptosis. So far, TL1A/DR3 interaction was shown to promote apoptosis only in experimental models of transient over-expression of DR3. In contrast, in primary T lymphocytes, the main pathway is the induction of pro-inflammatory signals. This seems to be mediated by the TL1A-induced production of cellular inhibitor of apoptosis proteins (c-IAP) that is upregulated by NF-κB. Therefore, a feedback loop is created that inhibits apoptosis and perpetuates T-cell co-stimulation. TL1A; TNF-like cytokine 1A, DR3; death receptor 3, TRADD; TNFR-associated death domain protein, TRAF; TNFR-associated factor, RIP; receptor-interacting protein, MAPK; mitogen-activated protein kinase, NF-κB; nuclear factor kappa-light-chain-enhancer of activated B cells, FADD; Fas-associated death domain, c-IAP; cellular inhibitor of apoptosis protein, Teff; T effector cells, Treg; T regulatory cells.