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The characteristics and pivotal roles of triggering receptor expressed on myeloid cells-1 in autoimmune diseases

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ABSTRACT

Triggering receptor expressed on myeloid cells-1 (TREM-1) engagement can directly trigger inflammation or amplify an inflammatory response by synergizing with TLRs or NLRs. Autoimmune diseases are a family of chronic systemic inflammatory disorders. The pivotal role of TREM-1 in inflammation makes it important to explore its immunological effects in autoimmune diseases. In this review, we summarize the structural and functional characteristics of TREM-1. Particularly, we discuss recent findings on TREM-1 pathway regulation in various autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), type 1 diabetes (T1D), and psoriasis. This receptor may potentially be manipulated to alter the inflammatory response to chronic inflammation and possible therapies are explored in this review.

1. Introduction

Autoimmune diseases are a family of chronic systemic inflammatory disorders, characterized by the dysregulation of the immune system which finally results in the break of tolerance to self-antigen. Fine-tuning the immune response is absolutely critical to prevent excessive inflammation and tissue damage in autoimmune diseases. Complex overlapping pathogenic pathways span multiple aspects of the immune system. A better understanding of these pathways has led to the development of pharmacologic therapies targeting specific elements of the immune system which play a role in disease pathogenesis.

Triggering receptor expressed on myeloid cells (TREMs) are a family of cell surface receptors that play important roles in innate and adaptive immunity. In a number of chronic inflammatory conditions and malignancies, TREMs has been implicated in disease severity and progression. Among them, TREM-1 (CD354) was the first identified. TREM-1 is a pivotal innate immune receptor, which acts to initiate inflammation or to amplify inflammatory responses by cross-talking with Toll like receptors (TLRs) and/or nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs). It was initially demonstrated that TREM-1 was predominantly associated with infectious diseases [1,2]. Indeed, TREM-1 receptor and its signaling pathways contribute to the pathology of several non-infectious acute and chronic inflammatory diseases.

Given the role that TREM-1 plays in the numerous inflammatory conditions, a large bulk of pre-existing data clearly identifies a key

Abbreviations: TREM-1, triggering receptor expressed on myeloid cells-1; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; IBD, inflammatory bowel disease; T1D, type 1 diabetes; TLRs, toll like receptors; NOD, nucleotide-binding oligomerization domain; NLRs, NOD-like receptors; DAP12, DNAX-activation protein 12; DCs, dendritic cells; ECs, endothelial cells; HMGB1, high-mobility group box 1; HSP70, heat shock protein 70-kDA; PGLYRP1, peptidoglycan recognition receptor 1; SSc, systemic sclerosis; RAGE, receptor for advanced glycation end-products; IIM, idiopathic inflammatory myopathy; PGRPs, peptidoglycan recognition proteins; CKD, chronic kidney disease; ZAP70, zeta-chain-associated protein kinase 70; SYK, spleen tyrosine kinase; Cbl, casitas b-lineage lymphoma; SOS, son of sevenless; GRB2, growth factor receptor binding protein-2; PI3K, phosphatidylinositol 3-kinase; PLC-γ, phospholipase-C-γ; Elk1, ETS domain-containing protein; NFAT, nuclear factor of activated T-cells; PRRs, pattern recognition receptors; PAMPs, pathogen-associated molecular patterns; CIA, collageninduced arthritis; JIA, juvenile idiopatic arthritis; BAFF, B cell-activating factor; CD, crohn's disease; UC, ulcerative colitis; MPO, myeloperoxidase; HLA, human leukocyte antigen; HIF-1α, hypoxia inducible factor-1α

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functional role for TREM-1 in numerous types of autoimmune diseases, including rheumatoid arthritis (RA) [3,4], systemic lupus erythematosus (SLE) [5–7], inflammatory bowel diseases (IBD) [8,9], type 1 diabetes (T1D) [10], and psoriasis [11]. Blockade of TREM-1 could be a novel therapeutic target in autoimmune diseases without impairing the host defense against microbes. The aim of this review was to discuss the state of the field of TREM-1 biology, including the structure and expression pattern of TREM-1, the putative ligands for TREM-1, TREM-1 signaling pathway and soluble TREM-1 (sTREM-1), etc. Furthermore, the strategy for TREM-1 blockade is also reviewed in context of developing novel therapeutics. Particular emphasis is placed on role of TREM-1 in autoimmune diseases and the challenges that remain in the treatment of autoimmune diseases up to date.

2. The characteristics of TREM-1

2.1. Structure and expression pattern of TREM-1

The gene encoding TREM-1 is mapped to human chromosome 6p21. TREM-1 is a 30 kD immunoglobulin superfamily member. Crystal structure data are inconclusive as to whether or not TREM-1 forms homodimers [12,13]. Human membrane TREM-1 is a 234 amino acid type I transmembrane protein consisting of a single extracellular immunoglobulin (Ig)-like domain (184 amino acids), a transmembrane region with a positively charged lysine residue, and a short cytoplasmic tail (5 amino acids) lacking any signaling motifs [14]. Recently, ectodomain of TREM-1 was shown be able to homooligomerize in a concentration-dependent manner, which suggests that the clustering of TREM-1 on the membrane promotes its oligomerization [15]. The transmembrane domain of TREM-1 mediates the formation of a complex with the signaling adaptor DNAX-activation protein 12 (DAP12). Moreover, DAP12 stabilizes TREM-1 surface expression and multimerization [15].

TREM-1 is widely expressed on myeloid cells, including neutrophils, a subset of monocytes, dendritic cells (DCs), and macrophages, in both membrane-bound and soluble form through alternative splicing or proteolytic cleavage [16,17]. In addition to myeloid cells, TREM-1 is also expressed on non-myeloid cell types including epithelial and endothelial cells (ECs) [18–20]. TREM-1 expression is significantly increased in infectious diseases [21,22] and non-infectious inflammatory diseases such as acute pancreatitis, inflammatory bowel diseases, gout and rheumatoid arthritis [23–25]. Therefore, TREM-1 expression is probably an important mediator of inflammation (Table 1).

TREM-1 itself can be up-regulated in response to LPS [1], TNFα [26], IL-1β, and PGE2 [19,27]. In a macrophage cell line, it has been shown that the expression of TREM-1 in response to LPS and bacteria *Pseudomonas aeruginosa* is inhibited by PGD2 and cyclopentanone prostaglandins PGJ2 and 15-dPGJ2 [28]. Moreover, cathelicidin peptide LL-37 was reported to down-regulate LPS-induced TREM-1 expression on monocytes [29]. Membrane binding TREM-1 expression was not altered by CpG-ODN alone but supernatant sTREM-1 level was increased in mouse macrophage cell line RAW 264.7 [6]. Whereas, macrophage stimulation with both LPS and CpG-ODN significantly abrogated TREM-1 LPS-induced membrane upregulation [6]. TREM-1 gene transcription is positively regulated though AP-1, cAMP, NF-κB, vitamin D receptor and hypoxia response elements [20,30–33]. Whereas, the transcription factor PU.1 acts as a brake to TREM-1 expression as TREM-1 expression is suppressed by PU.1 overexpression [31,34].

2.2. TREM-1 ligands

It has been postulated that TREM-1 recognizes soluble proteins or cell-surface proteins which are upregulated as a result of inflammation and/or tissue damage. Despite some recent evidence that high-mobility group box 1 (HMGB1), heat shock protein 70-kDA (HSP70), CD177 and peptidoglycan recognition receptor 1 (PGLYRP1) may potentially act as ligands for TREM-1, the actual nature of the TREM-1 ligand(s) and mechanisms of TREM-1 signaling are still unknown. Targeting these ligands with molecules that prevent specific ligand interactions with TREM-1 may prove to be of therapeutic use, contingent upon more focused pre-clinical testing.

Table 1
Abnormal expression of TREM-1 in inflammatory autoimmune diseases.

Disease	Species	Expression of TREM-1			Ref.
		mRNA	TREM-1	sTREM-1	
RA	Human	Synovium ↑	Synovia-CD45 ↑	Plasma ↑	[3]
	Human	SF-LEU ↑	ST ↑	SF ↑	[22]
	Human	ND	ST-CD14$^+$ ↑	ND	[96]
	Mouse	ND	ST-CD11b$^+$ ↑	ND	[96]
	Human	ND	ND	Plasma ↑	[101]
	Human	ND	ND	Serum ↑	[104]
SLE	Human	ND	ND	Serum ↑	[6]
	Human	ND	ND	Plasma ↑	[7]
	Human	ND	ND	Serum ↑	[118]
	Mouse	SP ↑, LN ↑	ND	Serum ↑	[118]
IBD	Human	IM ↑	Mø ↑	ND	[8]
	Mouse	CT ↑	CT ↑	ND	[8]
	Human	ND	Neu ↑, Mø ↑	ND	[9]
	Human	ND	ND	Serum ↑	[127]
	Human	ND	ND	Serum ↑	[128]
T1D	Human	ND	ND	Serum ↑	[10]
Psoriasis	Human	ND	LS-S ↑	Serum ↑	[11]

ST, synovial tissue; SF, synovial fluid; LEU, leucocyte; SP, spleen; LN, lymph nodes; Mø, macrophage; IM, intestinal mucosa; CT, colonic tissue; N, neutrophil; LS-S, lesional skin; ND, not determined.

2.2.1. Ligand on platelets

Platelets express a wide range of TREM receptors from which TREM-1 is critical for platelet function. Platelet-mediated augmentation of LPS-induced polymorphonuclear leukocyte activation is blunted by the presence of TREM-1 neutralizing antibody [35]. Multiple evidence point towards increased platelet activation in autoimmune diseases, including RA [36], systemic sclerosis (SSc) [37] and SLE. Activated platelets contribute to the maturation of DCs [38]. The maturation of DCs is crucial in the pathogenesis of SLE. Moreover, platelets themselves are a source of autoantigens involved in the formation of immune complexes [39]. Platelet autoantibodies were found in SLE patients [40].

TREM-1 ligand was detected on the cell surface of human platelets by using a recombinant soluble fusion protein consisting of the extracellular domain of human TREM-1 fused to the Fc part of human IgG (rsTREM-1) [35]. This defines that platelets not only express TREM receptors but also express TREM ligand(s). Interestingly, TREM-1 ligand was not found on neutrophils up till now. The ligand for TREM-1 on the surface of platelets interacted with TREM-1, amplified LPS-induced neutrophil activation [35]. Binding of the fusion protein to platelets was inhibited by competing soluble protein or LP17 [35]. However, the soluble TREM-1 construct did not activate platelets as determined by platelet-dependent aggregation and degranulation [35].

2.2.2. HMGB1

HMGB1 also named amphoterin, is a DNA-binding nuclear protein that interacts with nucleosomes, transcription factors and histones, to regulate transcription. During inflammation, HMGB1 is actively secreted by activated myeloid cells and is released by dying and necrotic cells [41,42]. HMGB1 can promote the pathogenesis of inflammatory and autoimmune diseases once it is in an extracellular location [41]. HMGB1 can interact with multiple immune sensors and receptors, including receptors for advanced glycation end products (RAGE) as well as TLR2, TLR4 and TLR9, leading to the activation of MAPKs and NF-κB

pathways [43]. TREM-1 and RAGE share many similarities. Direct interaction between purified murine TREM-1 and HMGB1 has been demonstrated by chemical cross-linking using dimethyl adipimidate and by surface plasmon resonance [44]. The results illustrate HMGB1 as one of the elusive TREM-1 ligands that may act as an endogenous agonist.

2.2.3. HSP70

HSP70 is one of the most frequently studied HSPs because of its potential anti-inflammatory properties. Intracellular HSP70 was found to inhibit the pro-inflammatory NF-κB signaling pathway [45]. Moreover, extracellular HSP70 was also shown to have anti-inflammatory effects through inhibition of MAPKs and NF-κB signaling pathways [46]. This inhibition leading to a lower production of IL-6, IL-8, and MCP-1 upon TNF-α stimulation of synoviocytes obtained from RA patients [46]. Nevertheless, exogenously expressed HSP70 stimulates proinflammatory responses in human monocytes and up-regulates IL-6, IL-1β, and TNF-α expression [47].

Of note, HSP70 seems to display several properties in numerous autoimmune conditions. The expression of HSPA1A gene (one of the HSP70 genes) was significantly up-regulated in patients with autoimmune diseases, e.g. SLE, SSc, and idiopathic inflammatory myopathy (IIM) compared to healthy controls [48]. The results suggest an involvement of the HSP70 genes in the pathology of studied autoimmune disorders. The level of extracellular HSP70 protein was increased in patients suffering from SSc and IIM as compared to controls [48]. Binding Immunoglobulin Protein (BiP) is a member of human HSP70 protein family. It has been identified as an important autoantigen for T and B cells. Serum titers of antibodies against mycobacterial HSP70 (MycHSP70) were significantly elevated in RA patients and correlated with serum anti-BiP antibody titers [49].

Previous studies showed that necrotic cell products (NCLs) prepared from LPS-stimulated THP-1 cells are able to induce pro-inflammatory response [44,50]. This effect was reduced by blocking HSP70 and/or TREM-1, most likely due to a reduction of the p38 MAPK pathway [50]. Both HMGB1 and HSP70 are induced in activated monocytes/macrophages and released from stressed or injured cells. It suggests that HMGB1 and HSP70 proteins in the NCL may activate TREM-1 and thus up-regulate the proinflammatory response in THP-1 cells [50]. However, HSP70 did not directly bind TREM-1 [44], which is in contrast to the direct interaction found in HMGB1 and TREM-1.

2.2.4. PGLYRP1

PGLYRP1 belongs to a family of PGN-recognition proteins (PGRPs) that is highly conserved among insects and mammals [51] and it is expressed in polymorphonuclear leukocytes and is freed from granules upon their activation [52]. PGLYRP1 contains a peptidoglycan binding domain and possesses bactericidal properties against Gram-positive bacteria more so than Gram-negative bacteria [52]. In Drosophila, PGRPs function as pattern recognition proteins that bind bacterial PGN and activate Toll and Imd pathways to initiate immune responses [53].

PGLYRP1 has been previously suggested to be a functional TREM-1 ligand to activate TREM-1 and enhance cytokine production in human neutrophils and macrophages, when multimerized or complexed with PGN [54]. PGLYRP1 and bacterially derived peptidoglycan form complexes that constitute a potent ligand capable of binding TREM-1 and inducing known TREM-1 functions [54]. PGLYRP1 combined with PGN triggers TREM-1 provides a novel mechanism for how bacteria induce TREM-1 activation. This may provide an explanation for why TREM-1 blockade reduces mortality in mouse models of sepsis [55], and also provides a new mechanism by which bacteria can trigger myeloid cells in innate immunity. Interestingly, PGLYRP1 must be multimerized to become a functional TREM-1 ligand, then leading to TREM-1 activation during bacterial infection [54]. Multimerization of PGLYRP1 is sufficient for TREM-1 activation bypass the need for peptidoglycan in myeloid cells and raises the possibility that TREM-1 activation also occurs in the absence of infections [54]. Mice lacking Pglyrp1 are more sensitive to colitis and variants in the PGLYRP1 gene are associated with ulcerative colitis in patients [56,57]. It remains to be investigated if this is due to the bactericidal properties of PGLYRP1 or its signaling via TREM-1 [58]. TREM-1 can act as TREM-1 ligand and induce the relative TREM-1 functions. Nevertheless, PGLYRP1 did not impact TREM-1 dimerization either to resting or LPS-simulated monocytes [15]. In chronic kidney disease (CKD) patients with poor oral health, sTREM-1 and PGLYRP1 are elevated, and they positively correlate with MMP-8 and IL-1β [59].

2.2.5. Other ligands for TREM-1

Apart from the above ligands for TREM-1, pathogens were shown to activate TREM-1-mediated signaling. In this context, exposure of human neutrophils to Marburg and Ebola virus resulted in phosphorylation of DAP12 [60]. In addition, TREM-1 blockade leads to the inhibition of cytokine production induced by Marburg and Ebola virus [60]. Moreover, CD177 (also known as NB1 or PRV-1) was identified as an endogenous TREM-1 ligand [61].

2.3. TREM-1signalling pathway

TREM-1 forms a “head-to-tail” dimer with an extracellular V-type immunoglobulin-like domain (Ig-V) comprising approximately 120 amino acids [13]. The Ig-V, providing two possible binding sites for ligands, is followed by a region of approximately 70 amino acids that link to the transmembrane part of TREM-1 [12]. Recently, novel data suggest that the TREM-1-mediated cellular response is correlated with its level of aggregation [15]. The TREM-1 receptor displays only a short cytoplasmic tail. TREM-1 has no cytoplasmic signaling domain of its own, rather its signal is transduced by the phosphorylation of DAP12. Recruitment of DAP12 to TREM-1 is characterized by positive-negative charge attraction at the transmembrane level [62]. TREM-1 and DAP12 complexes is stabilized through a unique electrostatic interaction between a negatively charged (−) aspartic acid in DAP12, and a positively charged (+) lysine in TREM-1 intracytoplasmic tail, which is necessary for signal transduction (Fig. 1).

After TREM-1 crosslinking, the cytoplasmic part of DAP12 containing ITAMs (immunoreceptor tyrosine-based activation motif) gets phosphorylated at its tyrosine residue [62,63], providing a docking site for protein tyrosine kinases: ZAP70 (zeta-chain-associated protein kinase 70) and SYK (spleen tyrosine kinase). SYK promotes the recruitment and tyrosine phosphorylation of adaptor complexes that contain Cbl (casitas b-lineage lymphoma), SOS (son of sevenless) and GRB2 (growth factor receptor binding protein-2), which results in downstream signal transduction through PI3K (phosphatidylinositol 3-kinase), PLC-γ (phospholipase-C-γ) and the ERK pathways [64]. Activation of these pathways leads to intracellular Ca^{2+} mobilization, rearrangement of the actin cytoskeleton and activation of transcription factors such as Elk1 (ETS domain-containing protein), NFAT (nuclear factor of activated T-cells), AP1, c-Fos, c-Jun and NF-κB [65] (Fig. 1).

Activation of TREM-1 leads to the production of multiple proinflammatory cytokines, chemokines as well as other inflammatory mediators such as MCP-1, MCP-3, IL-6, IL-8, MIP-1α and TNFα in vitro cultures and in disease models [2,8,26,54,66], and this response can synergize with innate immune stimuli to amplify inflammatory responses [2,67]. Uniquely, TREM-1 activation, as opposed to LPS, induced monocyte expression of M-CSF and osteopontin [68].

Simultaneously, the activation of TREM-1 increases the expression levels of co-stimulatory molecules such as MHC Class II molecules, CD86 and CD40 leading to the differentiation of monocytes into immature dendritic cells with subsequent improvement of the ability to elicit T- lymphocyte cell responses [69]. Therefore, the activation of TREM-1 may play a pivotal role in the development of autoimmune diseases. Recently, it has been shown that activation of TREM-1 does not depend on its level of expression at the membrane but rather on the valency of its cross-linking [15].

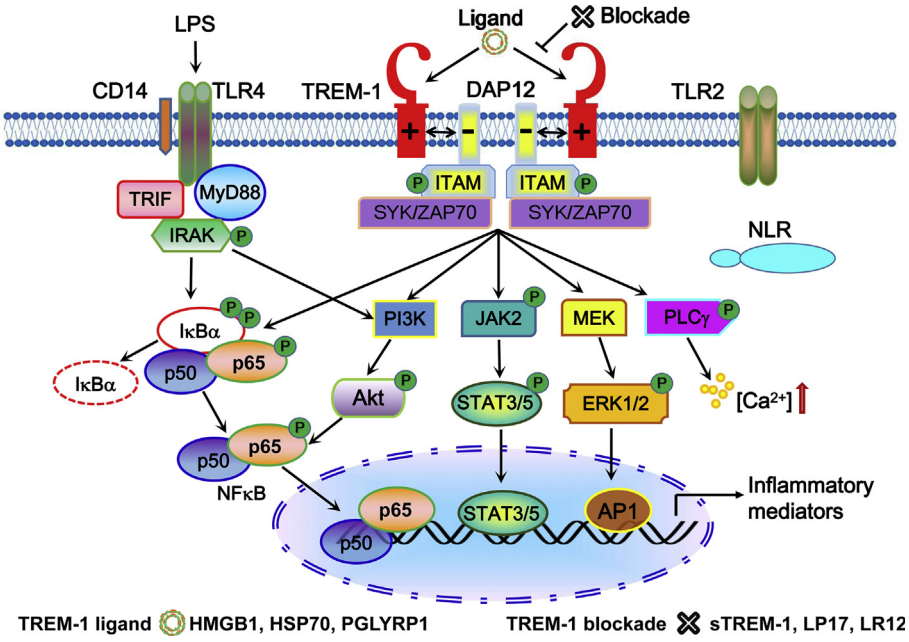

Fig. 1. Schematic representation of TREM-1/TLR4 pathway interaction.
TREM-1 associates with DAP12 via electrostatic interaction within the transmembrane domains. Upon binding to DAP12, the protein tyrosine kinases Syk and ZAP70 are recruited, results in phosphorylation of tyrosine residues within an ITAM motif of the DAP12 cytoplasmic domain, leading to the activation of PLC, PI3K, JAK and ERK pathways, upstream regulators of inflammatory gene transcription. The related signaling pathways regulate Ca^{2+} mobilization and gene transcription. Enhanced expression of inflammatory mediators amplifies the inflammatory response. Current approaches to blockading TREM-1 include the use of antagonists (LP17 and LR12) and a soluble TREM-1 receptor decoy. LPS binds to TLR4 and triggers the activation and translocation of the transcription factor into the nucleus where it induces the transcription of several pro-inflammatory. Dotted line lines illustrate protein degradation. TREM-1 signaling can also synergize with TLR4 cascade to amplify inflammation (details are explained in the text).

2.4. TREM-1synergizes with TLRs

TLRs belong to the family of pattern recognition receptors (PRRs) that recognize a wide range of pathogen-associated molecular patterns (PAMPs). A great set of data shows that TLRs emerge as promoters of chronic inflammation and play an essential role in the pathogenesis of autoimmune diseases [70–72]. In addition to induction of cytokine production by TREM-1 engagement alone, TREM-1 through combination with TLRs, and other pattern-recognition receptors synergistically increase the production of proinflammatory cytokines thus amplifying both innate and adaptive immune responses [73].

Activation of TREM-1 using agonistic monoclonal antibody was first reported to be combined with TLR4 ligands to synergistically amplify the production of proinflammatory cytokines in monocytes [66]. It makes TREM-1 an “amplifier” of inflammation. On the one hand, blockade of TREM-1 with an antagonistic peptide inhibited the LPS-induced TNF-α and IL-1β production in human monocytes [55,74]. On the other hand, TLR4 antagonist treatment inhibited the induction of TNF-α elicited by TREM-1 [74]. Interestingly, TREM-1 activation alone does not seem to induce sustained inflammation, which confirms that TREM-1 amplifies the inflammatory response initiated by TLRs engagement [1,75]. Nevertheless, TREM-1 engagement can also dampen expression of multiple LPS-induced genes, suggesting the complexity in the cross-talk between TLR4 and TREM-1 [68]. TREM-1 possesses the ability to amplify signaling not only by TLR4 but also by TLR2 [1,74]. Additionally, activation of TREM-1 is also shown to inhibit expression of Tollip and ST2, negative regulators of TLR-2 and TLR-4 pathways [76,77].

However, the molecular mechanisms leading to TREM-1-mediated amplification of the TLRs pathway are still being investigated. Intriguingly, stimulation of neutrophils with LPS or TREM-1 agonistic antibody leads to TLR4 and TREM-1 recruitment and colocalization in lipid rafts [78]. In addition, MyD88 was reported as an important point of crosstalk between TREM-1 and TLR4 signaling [79]. Synergistic production of pro-inflammatory mediators induced by simultaneous activation TREM-1 and TLR4 owing to PI3K, ERK1/2, IRAK1 and NF-κB activation [80](Fig. 1). However, available data suggest that the synergy appears to be cell-specific [16]. These studies collectively suggest that crosstalk between TLRs and TREM-1 is complex and may be at multiple levels.

TLRs also play an important role in enhancing TREM-1 expression [67]. Activation of TLR4 and TLR2 has shown to increase TREM-1 mRNA [26,31,81]. TREM-1 receptor expression is also upregulated after stimulation via LPS [26,66]. In a TLR-2 dependent manner, soluble fungal antigens were shown to up-regulate the expression of TREM-1 transcripts in macrophages [82]. Enhanced TREM-1 expression by TLR2 and TLR4 is MyD88-dependent and involves transcription factors NF-κB, PU.1 and AP1 [31,66,83,84]. CpG-ODN-elicited TLR9 activation of mouse macrophages induced a marked elevation of sTREM-1 level that is mediated by metalloproteinase-9 and inhibited by chloroquine [85]. Moreover, the shedding of sTREM-1 is increased following the stimulation via TLR4 [86]. Oppositely, TREM-1 silencing has no effect on TLR4 expression but down regulates several genes implicated in the TLR4 pathway including MyD88, CD14 and IκBα [87,88]. The results emphasize that regulating expression of downstream signaling molecules may be one of the mechanisms of TREM-1/TLRs crosstalk [87].

2.5. TREM-1 connects with NLRs

TREM-1 does not only synergize with TLRs, many recent studies support a model of synergy between TREM-1 and other PRRs, although the precise mechanisms are yet unclear. It will be important to clarify the mechanisms underlying the TREM-1/PRRs liaisons in detail. NLRs are members of the PRR family that can cooperate with TLRs, and regulate inflammatory and apoptotic responses. Among the NLRs, NOD1 and NOD2 are two well defined cytosolic PRR that are activated by molecules induced from dead or dying cells.

Rare data is obtained about the effect of TREM-1 and NLRs. In this respect, simultaneous activation of TREM-1 and NOD1/2 leads to phosphorylation of Akt and p38 MAPK and has a synergistic effect on the production of pro-inflammatory in monocytes [89,90]. TREM-1 activation was described to induce the expression of NOD2 combined with NF-kB activation and cytokine production like IL-1β [89]. It remains to be determined how TREM-1 and (other) NLRs interact in different levels and if this interaction is of significance compared to other synergistic pathways with TREM-1.

2.6. sTREM-1

One of the most intriguing features of the TREM-1 is the release of soluble form of TREM-1 [17]. The origin of sTREM-1 is controversial.

On the one hand, it is proposed that sTREM-1 results from alternative splicing of mRNAs producing secreted receptor isoforms [91]. On the other hand, some other reports suggest that sTREM-1 is liberated by the proteolytic cleavage of membrane-bound TREM-1 by matrix metalloproteinases [85,86]. Consistent with the latter hypothesis, sTREM-1 levels were decreased upon stimulation of human monocytes with LPS in the presence of metalloproteinase inhibitors [85,86].

Regardless of the origin, sTREM-1 has proven to be a valuable diagnostic and prognostic marker since it can be easily detected in biological fluid using immunochemical assays. Elevated levels of sTREM-1 have now been found in multiple infectious and chronic inflammatory diseases such as sepsis, pneumonia, inflammatory bowel disorders, inflammatory rheumatic disorders, and SLE, etc. Earlier studies mostly focused on the role for sTREM-1 in various infectious diseases. For example, sTREM-1 levels are elevated in sera from patients with sepsis and in bronchoalveolar lavage fluid from patients with bacterial or fungal pneumonia [23,24]. Moreover, sTREM-1 has been advocated as a prognostic marker for patients with septic shock [92].

In sterile inflammation, sTREM-1 has been described to increase during IBD, acute gouty inflammation, SLE and RA. Significantly higher levels of sTREM-1 in plasma [7] and in serum [6] were detected of lupus patients than matched healthy controls which indicated that sTREM-1 levels may be an additional useful marker of disease activity in these diseases. Serum sTREM-1 level is significantly elevated in patients with SLE irrespectively of the presence or absence of infection or fever [6]. It suggests that elevated levels of sTREM-1 have nothing to do with infection or non-infection. The data presented here demonstrate that sTREM-1 has a significant role in SLE. However, the biological relevance of sTREM-1 in sterile inflammation is still unclear.

Previous findings showed that recombinant sTREM-1 inhibits LPS-induced neutrophil oxidative burst and release of IL-8 [35]. Moreover, sTREM-1 is thought to negatively regulate TREM-1 receptor signaling through neutralization of the respective ligands and to inhibit the effect of TREM-1 activation [93,94]. At the same time, this soluble form shows the protective effect in mouse model of sepsis [95] and RA [96]. These data suggest that sTREM-1 may function as a counter-inflammatory decoy receptor and apparently exerts an anti-inflammatory effect.

3. Pivotal role of TREM-1 in autoimmune diseases

3.1. RA

Rheumatoid arthritis is a systemic autoimmune disease caused by various factors, and is characterized by chronic inflammation of synovial joints, which leads to progressive destruction of cartilage and bone causing damage to extra-articular tissue [97]. Overproduction of pro-inflammatory cytokines and chemokines are strongly associated with the pathology of RA [98]. Although TNF inhibitors have been widely used in the treatment of RA, substantial proportion (up to a third) of RA patients treated with TNF inhibitors fail to achieve complete remission [99]. RA patients treated with TNF inhibitors manifested serious bacterial infection and reactivation of latent tuberculosis [100]. Therefore, novel therapeutic molecule needs to be developed which reduces excessive inflammatory responses but allows sufficient control of infection.

Previous study has indicated that RA patients had higher sTREM-1 levels in plasma than healthy controls, and sTREM-1 levels in RA patients plasma were associated with the measures of disease activity, suggesting that sTREM-1 in plasma could have an important role in the inflammatory progression [3,101]. Early diagnosis and treatment of RA are associated with improved outcome with respect to control of disease activity and prevention of irreversible joint damage [102,103]. This has prompted a search for objectively measurable biomarkers of normal or pathogenic processes in RA and response to treatment [103]. Serum sTREM-1 level which correlated with titers of anti-CCP antibody, was significantly higher in the disease-modifying anti-rheumatic drug (DMARD)-naïve early rheumatoid arthritis (ERA) group compared to established RA group and normal control [104]. These results suggest that serum sTREM-1 may provide a novel biomarker for RA activity and early diagnosis of RA [104].

Similarly, abundant TREM-1 expression has been observed in synovial fluid and cells of patients with RA as well as in the murine model of RA (collageninduced arthritis, CIA) [3,96]. Synovial fluid TNFα and sTREM-1 levels correlated with each other, and sTREM-1 and leucocyte TREM-1 mRNA levels each correlated with SF leucocyte counts [22]. Furthermore, TREM-1 is highly expressed in $CD14^+$ cells in chronic RA and in animal models, correlating with an increased production of the inflammatory cytokines suggesting that blocking this pathway may be an important venue for the development of novel therapeutic strategies in RA [3]. TREM-1 is expressed in vivo on mDCs recruited to the hypoxic joints of juvenile idiopatic arthritis (JIA) patients, suggesting the potential relevance of this molecule as a marker of mDCs generated under hypoxic conditions [33]. The elevated expression of both sTREM-1 and cell surface in RA suggests that TREM-1 may contribute to the chronic inflammation associated with RA.

Activating TREM-1 induces the production of multiple proinflammatory cytokines, including TNF-α, IL-1β, and IL-8, which contribute to the inflammatory responses to the pathogenesis of RA [3]. TREM-1/DAP12 pathway has also been positively associated with RA [4,105]. TREM-1 activation in human monocytes can up-regulate the expression of co-stimulatory molecules leading to the differentiation of monocytes into immature dendritic cells, which can elicit T-cell responses. Thus, TREM-1 potentially participates in the adaptive immune response contributing to the pathogenesis of RA disease [26,66]. Additionally, TREM-1 activation synergizes with TLR ligands to amplify the inflammation.

TREM-1 blockade using a recombinant adenovirus encoding extracellular domain of TREM-1 or a synthetic TREM-1 antagonistic peptide significantly ameliorated the joint inflammation in mice with CIA [96], without affecting T cell and B cell immune responses to the inducing antigen [106]. TREM-1 blockade suppressed inflammatory responses but did not affect the capacity of immune systems to fight bacterial infection. Because of this advantage of TREM1, modulation of TREM-1 signaling might be effective and safe therapeutic strategy not only in infectious diseases but also in chronic inflammatory diseases such as RA [4].

Bone destruction is a prominent feature observed in the joints of RA patients which causes substantial morbidity [107]. Osteoclasts are the primary bone-resorbing cells and the essential role of these cells in RA bone destruction has been extensively studied and confirmed in experimental models of arthritis. TREM-1 stimulation suppressed osteoclastogenesis in synovial fluid macrophages of RA patients [108]. Therefore, TREM-1 acts as a negative regulator in human osteoclast differentiation and identifies a novel inhibitory mechanism of osteoclastogenesis that may be important during inflammation [108]. Surprisingly, murine osteoclastogenesis was not affected by TREM-1 stimulation [108].

3.2. SLE

Sensing of nucleic acids by pattern recognition receptors is the key for the initiation and development of SLE. TREM-1 is a novel innate immune receptor, which can amplify TLR-induced inflammatory responses. The role of dendritic cells, plasmacytoid cells, and neutrophils has been reported in the pathogenesis of lupus [109,110]. TREM-1 is mainly expressed on neutrophils and a subset of monocytes [35]. mDCs are critical for the induction of protective immunity to microbial invasion and the maintenance of self-tolerance [111]. Their functions are tightly regulated by a complex network of inhibitory and activating signals transduced by a defined repertoire of cell surface receptors [112,113], and dysregulated expression of these molecules may result

in an aberrant response characterized by amplification of inflammation and loss of tolerance [111]. Our recent report provides the first evidence that the surface expression of TREM-1 on myeloid DCs from spleen of MRL/*lpr* mice was enhanced when compared to wild type mice [114].

Activation of TREM-1 in human monocytes could upregulate the expression of co-stimulatory molecules such as MHC Class II molecules, CD86 and CD40 leading to the differentiation of monocytes into immature dendritic cells with subsequent improvement of the ability to elicit T- lymphocyte cell responses [69]. Furthermore, TREM-1-activated monocytes results in the production of multiple proinflammatory cytokines, chemokines as well as other inflammatory mediators [35].

A great set of data shows that TLRs are implicated in the pathogenesis of SLE by enhancing recognition of self-molecules [71,115]. TLR also play an important role in enhancing TREM-1 expression [67]. TREM-1 through combination with TLRs, and other pattern-recognition receptors synergistically increase the production of proinflammatory cytokines thus amplifying both innate and adaptive immune responses [73]. TLR9 has been implicated in the breakdown of immunologic tolerance to self-nucleic acids in SLE and the generation of anti-dsDNA and anti chromatin antibodies [116,117]. CpG-ODN-elicited TLR9 activation of mouse macrophages induced a marked elevation of sTREM-1 level that is mediated by metalloproteinase-9 and inhibited by chloroquine [85]. It suggests a possible pathway for increased release of macrophage TREM-1 through TLR9 activation that might play a role in innate immune response in SLE.

Significantly higher levels of sTREM-1 in plasma [7] and in serum [6,118] were detected of lupus patients than matched healthy controls. The data presented here demonstrate that sTREM-1 has a significant role in SLE. Serum sTREM-1 level is significantly elevated in patients with SLE irrespectively of the presence or absence of infection or fever [6]. It suggests that increased shedding of TREM-1 may occur in SLE and might play a role in the pathogenesis of autoimmune disorders such as lupus. Other data also indicated that sTREM-1 levels may be an additional useful marker of disease activity in SLE [7].

The development of anti-TREM neutralizing antibodies has opened new avenues as it has proved to be therapeutically efficacious in several models of inflammatory and autoimmune diseases [4,11]. Renal inflammation leading to organ dysfunction and end-stage disease is a common feature of SLE [119]. Increased knowledge of pathogenic mechanisms could greatly enhance prognosis and treatment of kidney diseases. Anti-glomerular basement membrane antibody (anti-GBM)-treated 129 × 1/svJ mice developed severe nephritis, where TREM-1 is upregulated in renal inflammation and plays a vital role in driving disease [120]. TREM-1 blockade with an inhibitory peptide, LP17, markedly inhibited proteinuria and renal disease as measured by glomerulonephritis class, severity of tubulointerstitial disease, crescent formation, and inflammatory cell infiltrates [120]. Thus, TREM-1 blockade might represent an effective novel strategy for immune-mediated renal diseases such as lupus nephritis [120].

TREM-1 mechanistic pathways may reveal a common element which would provide a powerful therapeutic target that can be exploited in treating SLE. However, the in vivo role of TREM-1 in inflammatory diseases is still controversial. Recent evidence has also shed light into the complex and dual role of this receptor [121]. It has been shown that TREM-1 overstimulation may also be required for protective anti-inflammatory responses. It has been shown that a moderate dose of TREM-1 siRNA improves mice survival during polymicrobial sepsis, whereas high-dose siRNA leads to full silencing of TREM-1, resulting in blunting neutrophil respiratory bursts and increasing mortality in mice [76,122].

In a recent study, Trem-1$^{-/-}$.lpr mice were established to investigate the role of TREM-1 in lupus [118]. It was demonstrated that TREM-1 deficiency augments lupus progression and provides an innovative role for TREM-1 in SLE [118]. Activation of membrane bound TREM-1 could suppress TLR9-induced B cell-activating factor (BAFF) expression in bone marrow-derived DCs of B6.lpr mice [118]. Moreover, levels of sTREM-1, which could act as an antagonist of the surface receptors by competing for ligand binding [1,2,17], were positively correlated with levels of BAFF in the sera of lupus patients and therefore increased sTREM-1 levels can promote BAFF expression and disease progression [118]. These findings suggest that sTREM-1 production may be used as a diagnostic marker and inhibition of sTREM-1 production may be a novel therapeutic target for combination therapy of SLE [118].

Therefore, better understanding the precise mechanisms by which TREM-1 regulates signaling cascades involved in inflammatory conditions will provide new and important insights into the potential to exploit inhibition of TREM-1 to regulate inflammation and immunopathogenesis in autoimmune disorders [96].

3.3. IBD

Inflammatory bowel disease refers to chronic, remitting-relapsing inflammatory disorders which is considered as an autoimmune disease caused by an abnormal immune reaction to intestinal bacteria that occurs in patients with genetic susceptibilities [123,124]. There are two main clinical forms of IBD, including Crohn's disease (CD) and ulcerative colitis (UC). A growing body of evidence suggests that TREM-1 is involved in the pathogenesis of IBD [8,121,125].

TREM-1 is generally under-expressed in the healthy intestine, which causes immune tolerance to intestinal bacteria and antigens [126]. TREM-1 expression is significantly up-regulated in mucosal lesions in mouse models of colitis and in patients with IBD [8]. TREM-1-expressing neutrophils and macrophages are increased in inflamed colonic biopsies from patients with UC or CD [9]. Engagement of TREM-1 by an agonistic specific antibody on intestinal macrophages from IBD patients enhances the secretion of proinflammatory mediators such as IL-6, TNF, MCP1/CCL2 and IL-8 [127]. Therefore, TREM-1 contributes to amplify chronic inflammation and IBD pathogenesis. The mean sTREM-1 level in patients with either UC or CD was significantly higher than in healthy controls [128]. Intriguingly, sTREM-1 was found to be more correlated with disease activity in those with UC in contrast to the results on patients with CD [128]. This data suggest that, while sTREM-1 shows promise as a potential marker for disease activity in IBD patients, especially those with UC [128].

The relationships between TREM-1 genetic polymorphisms and susceptibility to IBD and disease phenotypes were also investigated [129]. Their data indicate that all 3 TREM-1 SNPs (rs9471535, rs2234237, and rs3789205) were significantly associated with susceptibility to intestinal BD [129]. However, TREM-1 SNPs do not have a significant association with the development of Crohn's disease or ulcerative colitis [129]. A much larger sample size may be involved to exclude other possibilities.

Inhibition of TREM-1 activation by TREM-1-derived antagonistic peptide even attenuates the progression of established colonic inflammation [127]. Blocking TREM-1 by the administration of LP17 substantially attenuates clinical course and histopathological alterations in experimental mouse model of colitis [127]. PGLYRP-1 has been identified as the ligand for TREM-1. High PGLYRP-1 levels in biopsies of IBD patients correlate with increased secretion of proinflammatory cytokines [9]. Moreover, blocking TREM-1 dampens secretion of inflammatory mediators in a subgroup of patients with IBD with elevated PGLYRP-1 and myeloperoxidase (MPO), suggesting that TREM-1 blockade could be a treatment for IBD [9].

Autophagy plays a compensatory role in the pathogenesis of IBD [130]. It was confirmed that inhibition of TREM-1, either by LR12 or genetically with TREM-1 KO mice, attenuates the severity of experimental colitis [131]. Inhibition of TREM-1 restores impaired autophagy, reduced ER stress/UPR (unfolded protein response) and re-establishes homeostasis of the gut microbiota coupled with a decrease in inflammatory cell infiltration and IL-6 expression [131]. These findings

reinforce the idea that TREM-1 may represent a novel drug target for the treatment of IBD by modulating autophagy activity and ER stress [131].

3.4. T1D

Type 1 diabetes is an organ-specific autoimmune disease with a complex etiopathogenesis [132,133]. In-depth understanding of T1D pathogenesis and pinpointing pathways that influence the on-going destruction of β-cells is of utmost importance. Emerging evidence suggests a broad role of the innate immune system in acceleration and maintenance of β-cell destruction than hitherto assumed [134–136].

However, very little is known about the role of sTREM-1 and the TREM-1/DAP12 pathway in the pathogenesis of T1D. The gene that encodes TREM-1 is located on chromosome 6p21 near the major histocompatibility complex region encoding the human leukocyte antigen (HLA), which contributes about 50% of the genetic risk in T1D [137]. Levels of sTREM-1 were found to be significantly higher in newly diagnosed patients with T1D compared to the healthy siblings both in the univariate and multiple regression model (case status, gender, age, HLA-risk, season, and period of sampling) [10]. Nevertheless, this result points towards sTREM-1 as having a role in the pathogenesis of T1D [10]. Interference with the TREM-1/DAP12 pathway may help preserve the residual pool of functional β-cells post-onset [10].

3.5. Psoriasis

Psoriasis is a common inflammatory skin disease characterized by keratinocyte hyperproliferation, epidermal inflammation, and angiogenesis. Although the pathogenesis of psoriasis requires further clarification, previous studies showed that bacterial infection is an important factor that can trigger and exacerbate psoriasis [138,139]. The TREMs family interaction with microbial products makes it a strong candidate to target inflammatory diseases, for example psoriasis. TREM-1 has been identified in the circulation and lesions of psoriasis patients, and the expression of TREM-1 decreased after effective treatments for psoriasis [11]. TREM-1 blockade by TREM-1 fusion protein was linked to a decreased Th17 response, suggesting that TREM-1 blockade could reduce the effect of psoriatic DC activation of Th17 cells [11]. Moreover, psoriatic patients displayed elevated levels of circulating sTREM-1 [11]. A decrease in TREM-1$^+$ dermal cells and mRNA levels were observed in patients classified as responders to the NBUVB treatment [11].

Hypoxia inducible factor-1α (HIF-1α) participates in angiogenesis and inflammation in psoriasis. In another study, TREM-1 and HIF-1α are expressed on keratinocytes and could be upregulated by bacterial infection [140]. Furthermore, increased HIF-1α levels may be explained by way of a pathway in which TREM-1 activates PI3K [140]. It provides an important clue to understand the pathogenesis of psoriasis, in which HIF-1α is regulated by a TREM-1 signal pathway [140]. The discovery provides new insights into the possible mechanism of TREM-1 and HIF-1α in psoriasis.

However, the relationship of TREM-1 and psoriasis is controversial, especially in animal model of psoriasis. For example, TREM-1 deficiency did not induce any difference in T cell infiltration in the lesion as well as pathological features of psoriasis in a model of imiqimod (IMQ)-induced psoriatic lesion, an acute model of inflammation [141]. Also, TREM-1 signaling pathway enrichment was not significant in a dataset of skin tissue from the back of IMQ-treated wild type mice by silico analysis [141]. Altogether, these results suggest that future research should be conducted to investigate whether TREM-1 is a potential target in psoriasis.

4. TREM-1 Blockade: a novel therapeutic approach

Enhanced TREM-1 expression and activation were observed in several infectious and noninfectious inflammatory disorders, suggesting a pathogenetic role for this molecule. Several preclinical approaches have been developed for TREM-1 blockade, from genetic invalidation to the use of antibodies or decoy receptors, with the purpose of either identification of TREM-1 involvement in pathologies or treatment. A number of strategies have been developed to inhibit TREM-1 receptor activation using small molecules and peptides. Herein, we discuss the two potential peptides actually tested in preclinical studies.

4.1. sTREM-1

Soluble form of TREM-1 is proposed to act as an endogenous decoy receptor that binds TREM-1 ligands and prevents their engagement to membrane-bound TREM-1 [55,95]. The soluble receptors have limited use as therapeutic agents owing to their proning to high degradation. Nevertheless, sTREM-1 has been instrumental as the blueprint for the development of short inhibitory peptides, that may function as scavenger receptors to thwart ligands away from the ligand-binding domain of membrane-bound TREM-1,thus attenuating activation of TREM-1. In vivo modulation of TREM-1 by sTREM peptide might be a suitable therapeutic tool for the treatment of inflammatory diseases. Currently, these peptides are in an experimental phase, and some are under modification for potential use in clinical trials. Besides of sTREM-1, soluble form of RAGE can also act as decoy receptors for their respective ligands [43].

4.2. LP17

The generation of specific and short peptides bearing the same amino acid sequences in TREM-1 and TLT-1 (triggering receptor expressed on myeloid cells-like transcript 1) has been developed as antagonists of TREM-1 for their potential therapeutic applications [142]. A 17-amino acid peptide named LP17 (LQVTDSGLYRCVIYHPP) is a highly conserved sequence based on murine and human TREM-1, which is suitable as sTREM-1 mimics [55]. This peptide was shown to attenuate TNF-α and IL-1β production by human monocytes induced by LPS or TREM-1 agonistic antibody [55]. In this aspect, another finding reported that recombinant sTREM-1 inhibits LPS-induced neutrophil oxidative burst and release of IL-8, which support an anti-inflammatory role for sTREM-1 [35].

TREM-1 blockade has been already served as a therapeutic option in several animal diseases models using TREM-1 peptide LP17. Further studies in mice have also shown that in vivo administration of LP17 improved outcomes in rodent models of sepsis, inflammatory bowel disease, rheumatoid arthritis and cancer [25,95,96]. Since then, the therapeutic potential of LP17 in several infectious and non-infectious diseases has been investigated in experimental models.

4.3. LR12

LR12 (LQEEDAGEYGCM) is a 12-amino acid peptide derived from TLT-1. LR12 exhibit anti-inflammatory properties by dampening TREM-1 signaling and thus behave as naturally occurring TREM-1 inhibitors [143,144]. Indeed, LR12 does not directly bind to TREM-1 but to its endogenous ligand(s), acting as a decoy receptor. However, LR12 seems to specifically inhibit TREM-1 as this peptide shows no effect in the absence of TREM-1 [75,145]. TREM-1 multimerization at the cell surface is also mediated by its endogenous ligand. Therefore, the TREM-1 inhibitor LR12 can also limit TREM-1 multimerization [15].

The use of LR12 was able to protect against septic shock-induced cardiovascular dysfunction and organ failure and inflammatory response in murine and in minipigs [75,143]. In fine, antagonist administration improved survival [143]. In a recent study, it was demonstrated that TREM-1 is expressed by endothelial cells [146]. The pharmacological inhibition of TREM-1 by LR12 dampens vascular dysfunction induced by endotoxin or bacterial peritonitis [146].

Importantly, LR12 is able to mitigate endotoxin- induced inflammatory and clinical responses in nonhuman primates, without obvious side effects which pave the way for future phases Ia and Ib trials in humans [147]. Although not completely elucidated, these observations suggest that TREM-1 engagement plays an important role in sepsis.

Besides of sepsis, LR12 were also used in the treatment of other diseases. In LPS-induced mice ALI model, blocking TREM-1 by LR12 has protective effects against ALI by decreasing pulmonary inflammation and improving overall survival [148,149]. LR12 significantly reduced the proinflammatory cytokines (IL-6, IL-1β, and TNF-α) and chemokines (KC and MCP-1) production, whereas IL-10 was significantly increased by LR12 [149]. The protective effects by LR12 may be related to inhibition of NF-κB activation [148,149], ROS production [148], reduction of TREM-1 expression and increase of sTREM-1 release [149]. Pharmacological inhibition using LR12 dampens myocardial inflammation, limits leukocyte recruitment, and improves heart function and survival in mice or pigs [150]. Administration of LR12 improves hemodynamic parameters and cardiac function and limits remote organ dysfunction during cardiac ischemia in a clinically relevant porcine model of AMI [151]. Using LR-12 peptide also significantly reduced the development of atherosclerosis throughout the vascular tree, and lessened plaque inflammation [152].

The optimized HPLC-spectrofluorimetric method was successfully applied to determine LR12 concentration in an in vivo pharmacokinetic study in rats after intraperitoneal administration [153]. In order to protect LR12 from degrading and to prolong its release, in situ forming formulation is a suitable alternative for the therapeutic use of this peptide [154]. We believe that the use of the inhibitory dodecapeptide LR12, may provide extended benefit and will be worthy of clinical testing.

5. Conclusion and clinical perspectives

Accumulating data suggest that TREM-1 is commonly referred to as amplifier of inflammatory immune responses in the context with PRRs. Moreover, engagement of TREM-1 by itself can also lead to myeloid cell activation including the production of inflammatory cytokines and chemokines, and phagocytosis. A thorough characterization of TREM-1 will allow for a better understand of the role TREM-1 in autoimmune disorders associated with exaggerated inflammation (e.g., RA, SLE, IBD, etc.) and may represent a potential, novel target in these clinical conditions. In addition, a better identification of TREM-1 endogenous ligand will greatly advance our understanding of TREM-1 biology. Fortunately, numerous researchers have paid a lot of efforts to discover TREM-1 specific ligands. As we have summarized, some kinds of molecules are speculated to function as the endogenous ligands for TREM-1.

Soluble form of TREM-1 has already been described and shown to be biologically active. The presence of sTREM-1 in patients' fluids can be used as a possible indispensable biomarker for clinical applications. Although the origin and release mechanisms of sTREM-1 are still controversial, sTREM-1 was evidenced to counteract the pro-inflammatory signaling pathways which are activated following recognition of the TREM-1 receptor by its ligand. Whether soluble TREM-1 will function as a ligand for other receptors remains unknown. Membrane binding TREM-1 expression and sTREM-1 are elevated in diverse conditions. Immunoassays have been utilized in these trials to detect and measure protein levels of TREM-1 and sTREM-1 for prognostic and/or diagnostic value.

The challenge is to identify TREM-1 modulators that may be selective enough to apply as a treatment for any of these human diseases. TREM-1 inhibitory proteins, such as LP17 and LR12 are a promising class of compounds for the inhibition of unwanted inflammation during several non-infectious diseases. In many cases, TREM-1 intervention shows a beneficial effect in murine experiments. Nevertheless, the precise mechanism that underlies protection is unknown and mechanism-of-action should be further investigated. Additional evidence should also be obtained to support the application of TREM-1 in the treatment of clinical autoimmune diseases.

Disclosures

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