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# TREM and TREM-like Receptors in Inflammation and Disease*

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## Summary

Since the discovery of triggering receptor expressed on myeloid cells (TREM)-1 in 2000, evidence documenting the profound ability of the TREM and TREM-like receptors to regulate inflammation has rapidly accumulated. Monocytes, macrophages, myeloid dendritic cells, plasmacytoid dendritic cells, neutrophils, microglia, osteoclasts and platelets all express at least one member of the TREM family, underscoring the importance of these proteins in the regulation of innate resistance. Recent work on the TREM family includes: characterization of a new receptor expressed on plasmacytoid dendritic cells; definition of a key role for TREM in inflammatory bowel disease and multiple sclerosis; an expanded list of diseases associated with the release of soluble forms of TREM proteins; and identification of the first well characterized TREM ligand: B7-H3, a ligand for TREM-like Transcript (TLT)-2. Moreover, analysis of TREM signaling has now identified key regulatory components and defined pathways that may be responsible for the complex functional interactions between the TREM and toll-like receptors. In addition, there is expanding evidence of a role for TREM in the regulation of integrin function via Plexin-A1. Together these new findings define the TREM and TREM-like receptors as pluripotent modifiers of disease through the integration of inflammatory signals with those associated with leukocyte adhesion.

## Introduction

Innate immunity is critical for host survival during the early stages of infection. However, fine-tuning of this response is absolutely critical to prevent excessive inflammation and tissue damage. Pathogen sensing is achieved through a constellation of pathogen recognition receptors, such as the toll-like receptors (TLR)[1] (Box 1), which activate innate immune cells to clear the pathogen and to shape the adaptive immune response. Other innate immune receptors, such as the triggering receptor expressed on myeloid cells (TREM), modulate the innate response either by amplifying or dampening TLR-induced signals, and thus play critical roles in fine-tuning the inflammatory response. The TREM and TREM-like receptors are a structurally related protein family encoded by genes clustered on mouse chromosome 17C and human chromosome 6p21.1 (Figure 1). TREM and TREM-like receptors are expressed on a variety of innate cells of the myeloid lineage including neutrophils, monocytes, macrophages, microglia, osteoclasts, and dendritic cells, as well as on megakaryocytes and platelets. Thus far, TREM-like transcript (TLT)-2 expression on B and T lymphocytes is the only report of TREM family expression within the lymphoid lineage. The expression patterns of the TREM family proteins have recently been reviewed [1] and thus will not be addressed in detail here

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(Figure 1). Rather, we review recent developments in TREM and TREM-like disease associations, ligands, and signaling with the purpose of defining a common mechanism for their roles in immunobiology.

## TREM-Mediated Regulation of Inflammation

Initial findings established TREM-1 as an amplifier of the systemic inflammatory response syndrome associated with sepsis. During infection, receptor expression is modulated and soluble TREM-1 is released. In addition, administration of recombinant TREM-1/Fc fusion proteins or antagonistic peptides rescues mice from endotoxemia or polymicrobial sepsis [2-4]. Despite the apparent detrimental effects of over stimulation through TREM-1, recent findings suggest that some TREM-1 signal is necessary for successful antimicrobial responses. Gibot et al. found that a moderate dose of TREM-1 siRNA improved survival during polymicrobial sepsis in mice whereas high dose siRNA compromised neutrophil respiratory burst and increased mortality [5]. In contrast to polymicrobial sepsis, even full silencing of TREM-1 was protective in simple endotoxemia [5]. Thus, TREM-1 tunes the septic response in order to facilitate efficient clearance of the pathogen without damaging the host. Accordingly, recent evidence indicates that TREM-1 synergizes with LPS in the induction of some genes, but it can also dampen expression of multiple LPS-induced genes, suggesting an additional level of complexity in the cross-talk between TLR and TREM-1 [6].

In addition to a role for TREM-1 in sepsis, recent findings have linked TREM-1 to inflammatory bowel disease (IBD)[2]. While only a few TREM-1 expressing macrophages can be found in the normal colon, TREM-1 positive macrophages were readily detected in the lamina propria of patients with IBD, and engagement of TREM-1 on the surface of these macrophages resulted in enhanced production of TNF, IL-6, IL-8, and MCP-1 [7]. In mice, TREM-1 mRNA and protein were also absent in non-inflamed colon but increased during experimental colitis. Furthermore, administration of the antagonistic TREM-1 peptide LP17, even after colitis establishment, decreased disease severity [7]. These findings reveal an important role for TREM-1 in the establishment of IBD and suggest that targeting TREM-1 in the intestine could be beneficial for patients suffering from ulcerative colitis or Crohn's disease.

Unlike TREM-1, which is involved in the amplification of inflammation, TREM-2 is emerging as an important negative regulator of autoimmunity. Initial work established the ability of TREM-2 to suppress macrophage TNF and IL-6 production and to promote an anti-inflammatory state in microglia [8-10]. More recently, Piccio et al. have extended these observations by documenting that TREM-2 is upregulated on microglia and infiltrating macrophages in both the spinal cord and brain during experimental autoimmune encephalomyelitis (EAE)[3], the mouse model of multiple sclerosis (MS)[4] [11]. Administration of an antagonistic anti-TREM-2 prior to clinical onset induced more severe disease with earlier onset and a more symptomatic chronic phase [11]. In agreement with these findings, myeloid cells transduced with TREM-2 are more anti-inflammatory in vivo, traffic to the CNS and suppress EAE in mice [12]. In humans, TREM-2 is expressed by cerebrospinal fluid (CSF), but not blood, monocytes. Compared to patients with non-inflammatory neurological disease, those suffering from MS or other inflammatory neurological diseases had decreased percentages of TREM-2 positive monocytes in their CSF [13]. Moreover, TREM-2 was also found on the lipid-laden macrophages present within demyelinating MS lesions [13]. These cells clear myelin and cell debris from the CNS, are anti-inflammatory and are thought to promote resolution of CNS inflammation. Together these data solidify the role of TREM-2 as an important anti-inflammatory receptor and suggest that modulation of TREM-2 expression or function may be an important way to regulate CNS inflammation.

Loss of function mutations in TREM-2 or DAP12 result in Nasu-Hakola disease (NHD)[5], a rare disease characterized by dementia, bone cysts, and impaired osteoclastogenesis (reviewed in [14]). Like osteoclasts, multinucleated giant cells (MGC), which accumulate at sites of granulomatous inflammation, are formed by macrophage fusion. MGC formation in vitro is driven by IL-4 and this process was recently shown to be dependent on DAP12 [15]. Although DAP12 mutation affects multiple receptors, siRNA knockdown demonstrated that TREM-2, which is induced on macrophages by IL-4 [8], was the key receptor required for MGC development [15]. Therefore, in addition to its anti-inflammatory role, TREM-2 regulates macrophage fusion.

In the last year, a new TREM family member, PDC-TREM, has been characterized. PDC-TREM is not constitutively expressed but is induced following plasmacytoid dendritic cell (pDC) stimulation with CpG [16]. In contrast to Siglec H, which suppresses interferon production by pDC, PDC-TREM signals enhance interferon production [16,17]. These conflicting observations may be due to the timing of the DAP12 signal. Although both receptors couple to DAP12, SiglecH is constitutively expressed and therefore signals together with TLR-9 throughout the culture [18]. In contrast, PDC-TREM is inducible and thus CpG signals unabated for several hours before PDC-TREM-mediated signals are received [16]. Therefore timing may be critical in this positive amplification loop, suggesting that consideration of the timing of TREM and/or TREM ligand expression should be included in the interpretation of their interactions with TLR signals.

Similar to TREM-1 and PDC-TREM, TLT-1 and TLT-2 promote cellular activation, although neither of these receptors is coupled to DAP12 for signaling. Our laboratory recently showed that antibody directed against the extracellular domain of TLT-1 effectively inhibited human platelet aggregation in vitro [19] and we have recently confirmed a role for TLT-1 in platelet aggregation by characterizing TLT-1 null mice. Like TREM-1 and TREM-2, TLT-1 is also involved in inflammation as TLT-1 null mice show significant differences in their response to localized inflammation (Washington V. et al., unpublished). TLT-2 also appears to contribute to leukocyte activation even though the signaling pathway downstream of TLT-2 has not yet been characterized. Hashiguchi et al. recently demonstrated the ability of TLT-2 to co-stimulate T cells, resulting in enhanced CD3-mediated IL-2 and IFN-γproduction [20]. In vivo anti-TLT-2 or anti-B7-H3 reduced dinitroflourobenzene-induced contact hypersensitivity and hapten- specific IFN-γproduction [20]. Although TLT-1 is largely limited to platelets and megakaryocytes, TLT-2 is expressed not only on T cells but also on B cells and myeloid cells suggesting the in vivo effects of anti-TLT-2 may not be due solely to regulation of T cells.

## Soluble TREM (sTREM)

One of the most intriguing features of the TREM family is the release of soluble receptors. To date, soluble forms of three of the TREM family members (TREM-1, TREM-2, and TLT-1) have been detected. Soluble TREM (sTREM) has been detected in the biological fluids of patients and animals suffering from a variety of infections and diseases and often correlates with disease severity (Table I). Soluble forms of the other TREM receptors, including PDC-TREM and TLT-2, have not yet been described; however, based on the detection of three sTREM receptors thus far and the many disease states with which they are associated, it is likely that soluble versions of the other TREM will eventually be found.

The origin of sTREM is controversial. Since soluble versions of both DAP12-coupled (TREM-1 and TREM-2) and non-DAP12-coupled (TLT-1) receptors have been identified, DAP12 signaling is apparently dispensable for the production of sTREM. Some reports suggest that sTREM results from alternative splicing of mRNAs producing secreted receptor isoforms [21] while others propose that extracellular domains are cleaved off the cell surface. Consistent

with the latter hypothesis, sTREM-1 levels were decreased upon stimulation of human monocytes with LPS in the presence of metalloproteinase inhibitors [22]. Correspondingly, TREM-1 surface levels were increased in these same cultures, demonstrating reduced cleavage of membrane-bound TREM-1 in the presence of metalloproteinase inhibitors. The prevention of sTLT-1 and sTREM-2 generation by protease inhibitors has not yet been examined.

Although the function of sTREM is unknown, sTREM-1 and sTREM-2 are thought to negatively regulate TREM receptor signaling through neutralization of the respective ligands. Soluble mouse TREM-1 provides protection during sepsis [4] and blockade of TREM-2 exacerbates disease in a mouse model of MS [11]. Therefore, increased levels of sTREM-2 in the CSF of MS patients would be predicted to worsen the disease by interfering with TREM-2 signaling [13]. In contrast to sTREM-1 and sTREM-2, which can act as decoy receptors, murine sTLT-1, like TLT-1, enhances platelet activation (Washington V. et al., unpublished).

## TREM ligands

In order to truly appreciate the function of the TREM and TREM-like receptors and the contributions they make during inflammation and homeostasis, discovery of their ligands is crucial. Using recombinant TREM-1 fusion protein, TREM-1 ligands have been detected on the surface of murine neutrophils and human platelets. Gibot et al. found that the ligand was present on neutrophils during endotoxemia [23]. In contrast, the TREM-1 ligand on platelets was expressed under both resting and thrombin-activated conditions and TREM-1/ligand interactions enhanced LPS-induced respiratory burst and IL-8 production by PMN [24]. Although the identity of this ligand remains unknown, it is unlikely to be TLT-1 since TLT-1 is only weakly expressed on the surface of resting platelets and is dramatically upregulated by thrombin [25]. Putative TREM-1 ligands have also been reported to be present in the lysates of necrotic cells and in the serum of patients with sepsis [26,27]. El Mezayen et al. found that necrotic cell lysates (NCL), generated from LPS-stimulated THP-1 cells, synergized with LPS in the induction of pro- inflammatory cytokines [26]. Addition of TREM-1/Fc chimera to the cultures inhibited NCL-induced but not LPS-induced cytokine production suggesting that a TREM-1 ligand(s) was present in the NCL.

The same methodologies used to find TREM-1 ligands have been applied in the search for TREM-2 ligands. Using a TREM-2/Fc chimera, Hammerman et al. reported a TREM-2 ligand on the surface of peritoneal and bone-marrow derived macrophages [9]. TREM-2 also reportedly binds anionic ligands on the surface of Gram-positive and Gram-negative bacteria, including *Neisseria gonorrhoeae*, as well as an unidentified ligand present on human astrocytoma cell lines [28,29]. Recently, Piccio et al. confirmed the presence of a TREM-2 ligand on the astrocytoma cell line HTB12, fueling speculation that the interaction of TREM-2 on microglia with the TREM-2 ligand present on astroctyes may be responsible for the protective role of TREM-2 observed in EAE [11]. A confounding factor in identifying TREM-2 and PDC-TREM ligands is the finding that these TREM form a receptor complex with Plexin-A1. Although Plexin-A1 binds its ligand Sema6D independently of its interactions with TREM, engagement of Plexin-A1 by Sema6D results in DAP12 phosphorylation indicating that these TREM participate in Plexin-A1 signaling [16,30]. Whether putative TREM ligands cooperate with Sema6D in the activation of the TREM/Plexin-A1 receptor complexes or the TREM simply function as orphan signaling components of these complexes remains unclear. Nevertheless, future approaches aimed at identifying TREM ligands may need to consider the possibility that the TREM can operate as signaling components of multimeric receptor complexes.

In contrast to the approaches used to find the TREM-1 and TREM-2 ligands, a unique methodology was used to identify the TLT-2 ligand, which is the only fully characterized

TREM ligand identified to date. As part of an effort to find a receptor for the B7 family member B7-H3, Hashiguchi et al. discovered significant homology between CD28 family members, known receptors for other B7 molecules, and TLT-2, leading them to investigate the binding of B7-H3 to TLT-2 [20]. Indeed, B7-H3Fc bound to TLT-2 transfected cells and could be blocked by antibodies to either B7-H3 or TLT-2. Future attempts to identify TREM ligands may benefit from bioinformatic approaches similar to that taken by Hashiguchi and colleagues.

## TREM Signaling

Several TREM (TREM-1, TREM-2, TREM-3, and PDC-TREM) physically associate with the signaling chain DAP12, which contains a canonical immunoreceptor tyrosine-based activation motif (ITAM)[6] in its cytoplasmic domain. While the downstream signaling and functions of TREM-3 are unknown, the pathways triggered by TREM-1, TREM-2 and PDC-TREM are beginning to be elucidated. In monocytes, the non-T cell activation linker (NTAL/LAB) has recently been shown to promote TREM-1-mediated calcium mobilization while repressing Erk activation and the synergistic production of TNF and IL-8 by LPS and anti-TREM-1 [31]. In contrast, we have found that in macrophages, NTAL/LAB also represses TREM-2-mediated tyrosine phosphorylation while it is required for TREM-2 activation of Erk1/2. Moreover, altered TREM-2 signaling in NTAL/LAB$^{-/-}$ macrophages results in cells skewed toward the type II phenotype[7] with reduced TLR-induced expression of IL-12p40 and enhanced production of IL-10 (Whittaker et al., unpublished). These data suggest that manipulation of TREM signaling in various immune lineages leads to diverse outcomes. Recent data show that more distal TREM-1 signaling in dendritic cells requires caspase-recruitment domain protein (CARD)[8]-9 for the activation of NF-κB[9] and production of cytokines [32]. The CARD9 complex is also required for cytokine production following TLR stimulation of DC, suggesting a potential integration point between TREM and TLR signaling.

As mentioned previously, TLT-1 and TLT-2 do not couple to DAP12 for signaling. Rather TLT-1 has an ITIM[10] motif and interacts with the SH2[11] domain-containing protein phosphatases SHP-1 and SHP-2 [33,34]. New data from our laboratory suggest that TLT-1 binds ezrin, radixin, and moesin (ERMs) via their amino terminal FERM domains (Washington V. et al., unpublished) (Figure 2). This newly described ability of TLT-1 to bind to proteins associated with adhesion and cytoskeletal organization is consistent with the proposed role for TLT-1 in platelet aggregation [19]. Although no other TREM or TREM-like receptors are reported to interact directly with the ERMs, two other family members have now been shown to associate with proteins that regulate adhesion. Both TREM-2 and PDC-TREM interact with Plexin-A1, a protein that through its cytoplasmic GTPase domain mediates the suppression of R-Ras, resulting in inactivation of integrins, release from extracellular substrates, and cell collapse in fibroblasts [16,30,35]. Through this mechanism, plexins facilitate cell movement in the presence of their ligands and cell arrest once those ligands are no longer detected. Plexin-A1 engagement by Sema6D induces DAP12 phosphorylation, providing a direct link between TREM signaling and regulation of cellular adhesion and/or motility [30]. Thus a key role of TREM/DAP12 signaling may be activation of pathways associated with cell motility. Although plexin engagement leads to DAP12 phosphorylation, modification of plexin function in response to stimulation of TREM-2 or PDC-TREM has not been reported. Therefore, further dissection of the integration of TREM, Plexin, and integrin signaling in myeloid cells is clearly warranted and may provide considerable insight into the biological role of TREM in the regulation of inflammation.

## Conclusions

Despite the diversity of biological responses regulated by the TREM and TREM-like receptors, examination of the family has revealed several common characteristics that suggest unifying

themes for the family. First and foremost is the role of TREM in the integration of pathways associated with an inflammatory response (Figure 3). TREM-1, -2, and PDC-TREM all participate in the regulation of TLR responses, perhaps through modification of the CARD complex or the activation of ERK. In addition, TLT-1 and TLT-2 cooperate with platelet agonists and CD3, respectively. These observations suggest that the primary role of all TREM is in the tuning and integration of multiple signals rather than the direct initiation of a response. Such a hypothesis is in accordance with previous reports of crosstalk between DAP12 and diverse receptor systems such as the RANK[12] or Janus kinase[13] pathways [36,37]. Second, it is very likely that all TREM and TREM-like receptors will release a soluble isoform. Soluble forms of TREM-1, -2, and TLT-1 have already been described and two of the three have been shown to be biologically active. Whether soluble TREM isoforms will function as ligands for other receptors or as competitive inhibitors remains unknown, but it is tempting to speculate that soluble forms may extend the influence of all TREM outside of the cell types that express them. Lastly, data linking TREM-2, PDC-TREM, and TLT-1 to pathways regulating cellular adhesion suggests that the TREM family receptors may affect adhesion and/or trafficking. Such a hypothesis is consistent with previous descriptions of DAP12 phosphorylation during adhesion of macrophages and neutrophils and the reported adhesion defects of DAP12$^{-/-}$ macrophages [36,38]. Thus we propose that the diverse biological effects of the TREM family are mediated, in part, through the integration of inflammatory signals with those generated during immune cell interactions with one another or the extracellular matrix.

**Box 1**

Glossary terms

Toll-like Receptors (TLR), [1]germline-encoded receptors that recognize pathogen associated molecular patterns. TLR signals result in the activation of cells and the production of pro-inflammatory mediators.

Inflammatory Bowel Disease (IBD), [2]a group of intestinal disorders characterized by chronic inflammation of the bowel. Ulcerative colitis and Crohn's disease are the two most common types of IBD.

Experimental Autoimmune Encephalomyelitis (EAE), [3]a murine model of MS induced by injection of myelin proteins. EAE can be either acute or chronic-relapsing, and like MS, EAE also results in demyelination.

Multiple Sclerosis (MS), [4]an autoimmune disease in which the body's immune system attacks and damages the myelin sheath surrounding the nerves resulting in loss of muscle control.

Nasu-Hakola Disease (NHD), [5]also called PLOSL or polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy. NHD is a rare disease endemic to Japan and Finland resulting from loss of function mutations in *TYROBP* (DAP12) or *TREM2* (TREM-2). Patients suffer from presenile dementia, bone cysts, and osteopetrosis.

ITAM, [6]Immunoreceptor tyrosine-based activation motif. This receptor motif is characterized by two tyrosines ($Y_{XX}I/L_{\ x6\text{-}8}\ Y_{xx}\ I/L$) precisely spaced and in the configuration for phosphorylation. When phosphorylated, these tyrosines provide the docking site for the SH2-domain containing tyrosine kinases Syk or Zap70.

Type II macrophages, [7]sometimes referred to as alternatively activated macrophages. Whereas classical macrophages (type I) are activated by interferon gamma and LPS, type II macrophages are typically activated by IL-4 or IL-13. Type II macrophages secrete anti-inflammatory cytokines, such as IL-10, while type I macrophages produce pro-inflammatory cytokines, such as IL-12. This cytokine profile makes type II macrophages ideally suited for elimination of extracellular parasites and for wound healing and tissue repair.

CARD Complex, [8]A complex composed of the caspase recruitment domain-containing proteins Bcl10, Malt1, and either CARD9 or 11. The CARD11 (CARMA1) complex

couples ITAM signaling to NF-κB in T cells and B cells. The CARD9 complex appears to couple ITAM signals to NF-κB in myeloid cells. The CARD9 complex also is involved in facilitating the activation of Erk downsteam of TLR stimulation in DC.

NF-κB, [9]Nuclear factor kappa B. A widely expressed transcription factor involved in the production of multiple inflammatory mediators.

ITIM, [10]Immunoreceptor tyrosine-based inhibitory motif. A structural motif including a single tyrosine usually positioned two residues downstream and three residues upstream of a hydrophobic amino acid. When phosphorylated, this motif recruits SH2-domain containing protein tyrosine phosphatases.

SH2 domains, [11]Src homology 2 domains. These structural motifs form deep binding pockets that mediate specific binding of phosphotyrosine residues. Amino acids flanking a phosphotyrosine residue in a target protein determine the binding specificity by interacting with residues on the surface of the SH2 domain. SH2-mediated interactions direct many events associated with phosphotyrosine based signaling.

RANK, [12]The receptor for activation of NF-κB. RANK is a member of the TNF superfamily of receptors that is critical for the development of osteoclasts from myeloid precursors. RANK signaling leads to DAP12 phosphorylation, calcium mobilization, and induction of the transcription factor NFAT. The activation of NFAT is absolutely required for the development of osteoclasts.

Janus kinase, [12]a family of non-receptor tyrosine kinases utilized by cytokine receptors to initiate cellular signaling cascades. Janus activation leads to the recruitment and phosphorylation of signal transducers and activators of transcription (STAT).

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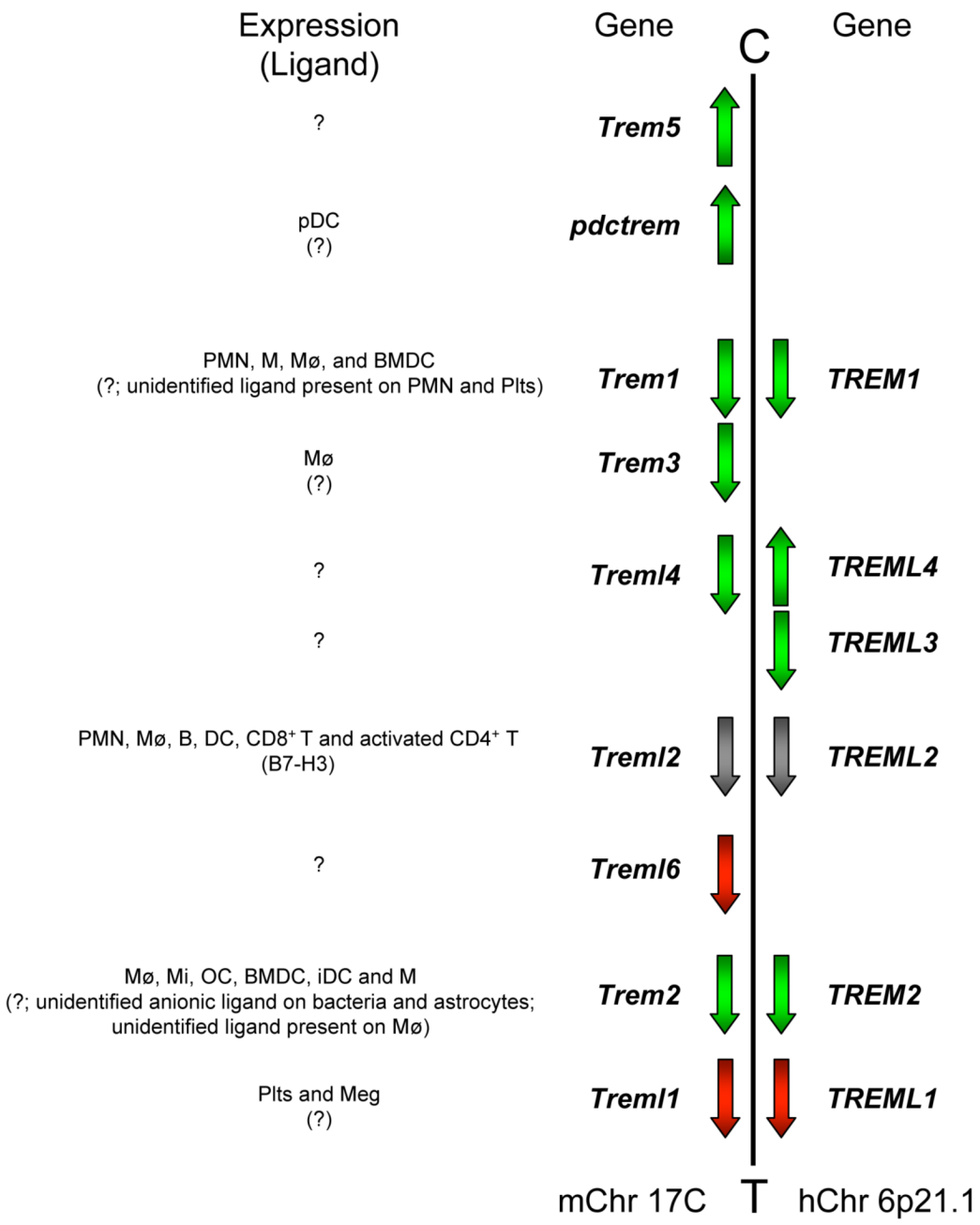


**Figure 1.**

Figure 1. TREM Family of Receptors. Localization of TREM genes on mouse chromosome 17C (left) and human chromosome 6p21.1 (right). Genes shown in green are either known or predicted to associate with DAP12. Those shown in red contain an ITIM motif(s). *Treml2*, shown in gray, neither associates with DAP12 nor has an ITIM. Where known, TREM expression is indicated. pDC (plasmacytoid dendritic cells), PMN (polymorphonuclear leukocytes), M (monocytes), Mφ(macrophages), BMDC (bone marrow-derived dendritic cells), B (B lymphocytes), DC (dendritic cells), iDC (immature dendritic cells), T (T lymphocytes), Mi (microglia), OC (osteoclasts), Plts (platelets), Meg (megakaryocytes). Ligand identity or lack thereof is listed in parentheses underneath the cell type(s) expressing

TREM. Diagram is representative of TREM chromosomal location but is not drawn to scale. C and T define the centromeric and telomeric ends of the chromosome, respectively. See text for references regarding the expression profiles of the TREM.

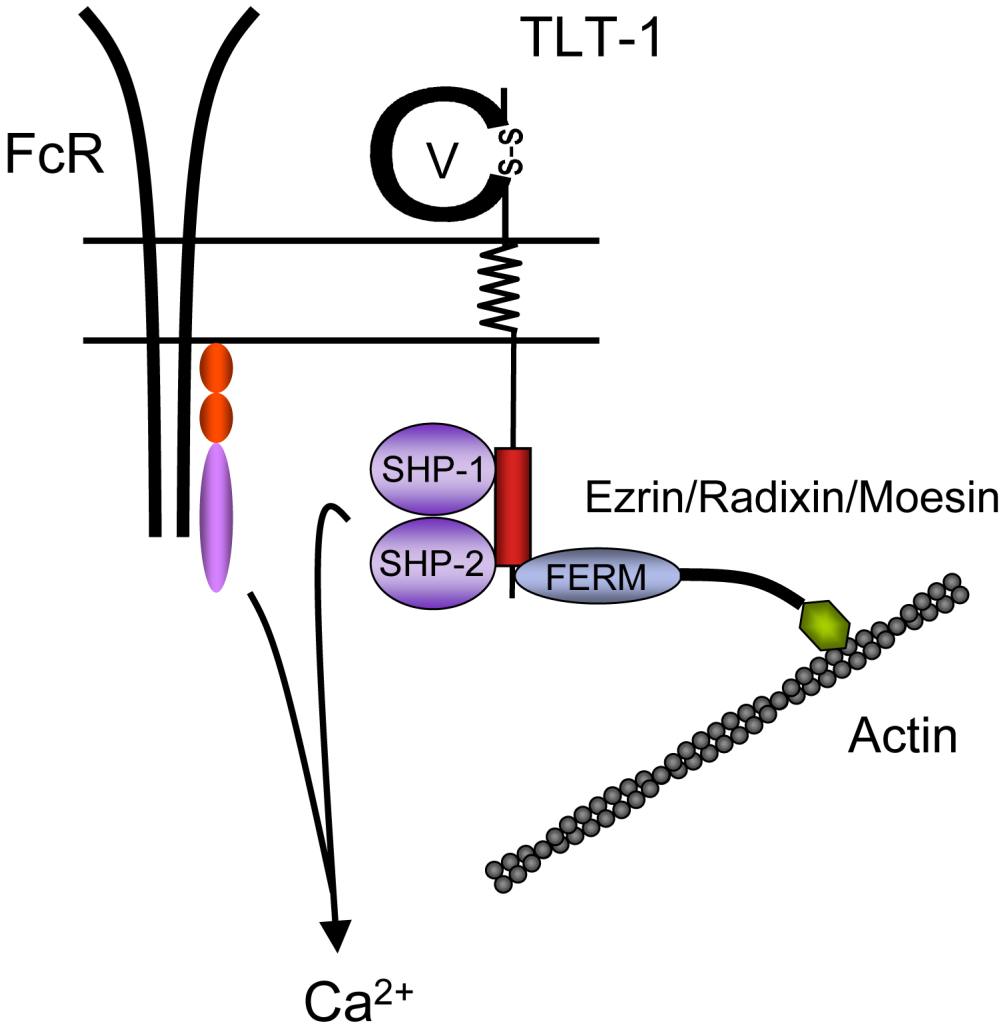


**Figure 2.**
TLT-1 Signaling Intermediates. The cytoplasmic domain of TLT-1 has an ITIM (red box) that when phosphorylated binds both SHP-1 and SHP-2 protein phosphatases. In transfectants, binding of SHP-2 by TLT-1 potentiates Fc receptor (FcR) signaling through an unknown mechanism. The carboxyl-terminus of TLT-1 also binds the FERM domains of Ezrin, Radixin, and Moesin in platelets. These ERMs couple integral membrane proteins to the actin cytoskeleton, providing a mechanism for TLT-1-mediated enhancement of platelet aggregation.

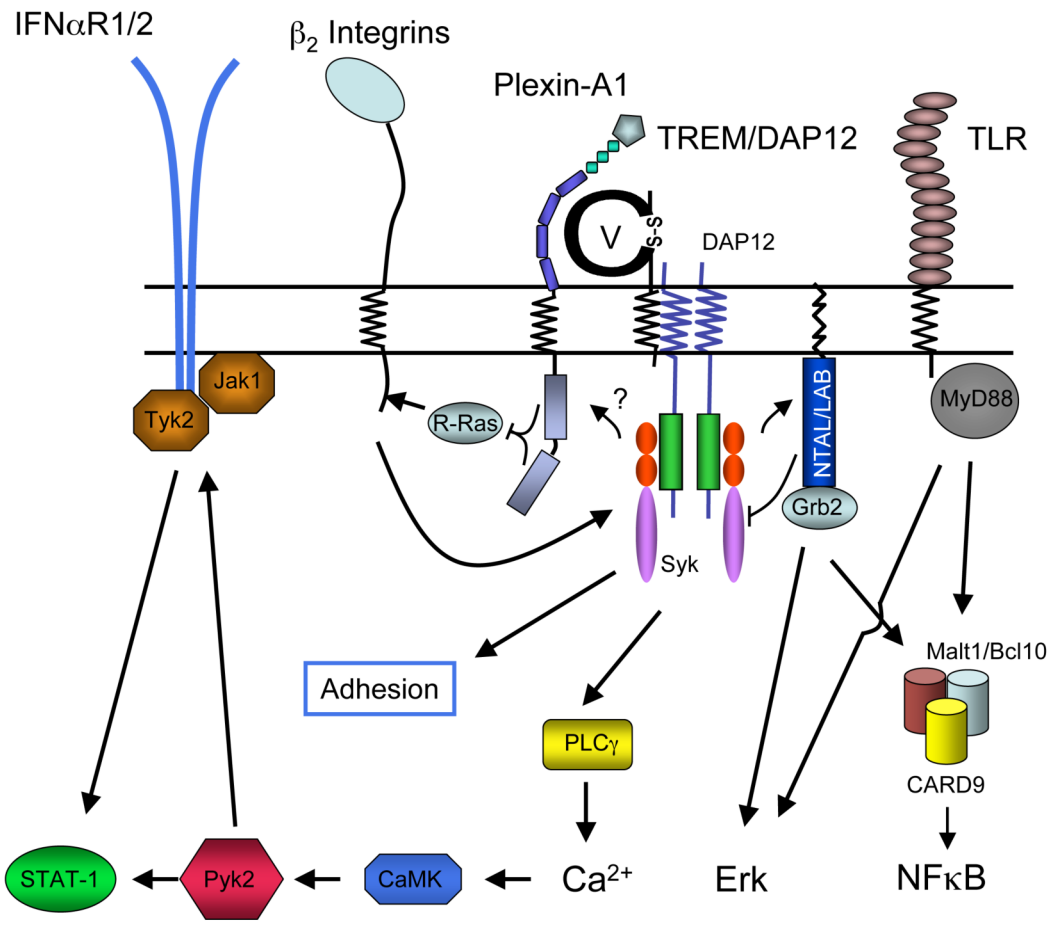


**Figure 3.**

Potential Networks of TREM Crosstalk with Multiple Immune Signaling Pathways. Engagement of DAP12-coupled TREM leads to phosphorylation of DAP12 on its cytoplasmic ITAM (Green boxes) and recruitment of the kinase Syk. Both TREM-1 and -2 also lead to Syk-mediated phosphorylation of the adaptor NTAL/LAB. NTAL/LAB negatively regulates TREM signals, including Syk activation and calcium mobilization, although its effects on Erk are controversial. Although the mechanism of interaction between TREM and TLR signaling remains unknown, both receptor systems activate Erk and can utilize the Malt1/Bcl10/CARD9 complex to stimulate NF-κB, suggesting regulation of this complex may be critical in understanding how TREMs can either accentuate or repress TLR responses, depending on cellular context. Integrin engagement leads to DAP12 phosphorylation, resulting in calcium mobilization and activation of calcium activated protein kinase (CaMK). Although it is not known whether TREM-associated DAP12 is the target of integrin signaling, CaMK, via the tyrosine kinase Pyk2, enhances the expression of STAT-1 and potentiates the activation of STAT-1 downstream of type I interferon receptors, providing a potential mechanism for TREM modification of cytokine signaling. TREM-2 and PDC-TREM also physically interact with Plexin-A1, suggesting they form a feedback loop for the regulation of integrins. Phosphorylation of Plexin-A1, possibly via Fes, Fyn, or DAP12-associated Syk, modifies the RasGAP activity of its cytoplasmic tail, leading to suppression of R-Ras and reductions in integrin affinity. Therefore, DAP12-coupled TREM have the potential to modify TLR, cytokine, integrin, and ITAM signaling, but more work is needed to fully understand these interactions.

**Table I**

**TREM and TREM-like Receptors in Disease**

TREM message, TREM protein, and sTREM levels are elevated in many inflammatory diseases in both mouse and human. Where indicated, the biological fluids/tissues in which TREM was measured are shown in parentheses. Abbreviations used: ND, Not Determined; BAL, Bronchoalveolar Lavage Fluid; CSF, Cerebrospinal Fluid; COPD, Chronic Obstructive Pulmonary Disease; CAP, Community Acquired Pneumonia; VAP, Ventilator-Associated Pneumonia; IBD, Inflammatory Bowel Disease; NSCLC, Non-small Cell Lung Cancer; TAM, Tumor-Associated Macrophages; CF, Cystic Fibrosis; NHD, Nasu-Hakola Disease; MS, Multiple Sclerosis; OIND, Other Inflammatory Neurological Disease; EAE, Experimental Autoimmune Encephalomyelitis.

| Disease | TREM message | TREM protein | sTREM | Species | References |
|---|---|---|---|---|---|
| ***TREM-1*** | | | | | |
| COPD | ND | ND | Increased (Serum) | Human | [39] |
| CAP | ND | Increased (BAL) | Increased (Serum,BAL) | Human | [40-42] |
| VAP | ND | ND | Increased (BAL) | Human | [41,43] |
| Pulmonary Aspiration Syndrome | ND | ND | Increased (BAL) | Human | [44] |
| Exudative Pleural Effusions | ND | Increased | Increased (Pleural) | Human | [45,46] |
| Acute Pancreatitis | Increased | ND | Increased (Serum) | Human | [47,48] |
| Peptic Ulcer Disease | ND | ND | Increased (Gastric) | Human | [49] |
| IBD | Increased (intestinal mucosa) | Increased (lamina propria) | Increased (Serum) | Human | [7,50,51] |
| | Increased (colon) | Increased (colon) | ND | Mouse | [7] |
| Sepsis | Increased | Increased | Increased (Plasma) | Human | [2,4,52-55] |
| | Increased | Increased | Increased (Plasma, Serum, Peritoneal) | Mouse | [3-5] |
| Gout | Increased (Pouch) | Increased (Pouch) | Increased (Pouch) | Mouse | [56] |
| NSCLC | ND | Increased (TAM) | Increased (Pleural) | Human | [57] |

| Disease | TREM message | TREM protein | sTREM | Species | References |
|---|---|---|---|---|---|
| CF | ND | Decreased (Monocytes) | No Change (Serum) | Human | [58] |
| ***TREM-2*** | | | | | |
| NHD | Decreased | Decreased | Decreased | Human | [59] |
| MS/ OIND | ND | Decreased (CSF) | Increased (CSF) | Human | [13] |
| EAE | Increased (spinal cord, brain) | Increased (spinal cord) | ND | Mouse | [11] |
| ***TLT-1*** | | | | | |
| Sepsis | ND | ND | Increased (plasma) | Human | Washington V et al., unpublished |
| | ND | No Change | Increased (plasma) | Mouse | Washington V et al., unpublished |