Review

TREM2-Ligand Interactions in Health and Disease

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Abstract

The protein triggering receptor expressed on myeloid cells-2 (TREM2) is an immunomodulatory receptor with a central role in myeloid cell activation and survival. In recent years, the importance of TREM2 has been highlighted by the identification of coding variants that increase risk for Alzheimer's disease and other neurodegenerative diseases. Animal studies have further shown the importance of TREM2 in neurodegenerative and other inflammatory disease models including chronic obstructive pulmonary disease, multiple sclerosis, and stroke. A mechanistic understanding of TREM2 function remains elusive, however, due in part to the absence of conclusive information regarding the identity of endogenous TREM2 ligands. While many TREM2 ligands have been proposed, their physiological role and mechanism of engagement remain to be determined. In this review, we highlight the suggested roles of TREM2 in these diseases and the recent advances in our understanding of TREM2 and discuss putative TREM2–ligand interactions and their potential roles in signaling during health and disease. We develop a model based on the TREM2 structure to explain how different TREM2 ligands might interact with the receptor and how disease risk variants may alter ligand interactions. Finally, we propose future experimental directions to establish the role and importance of these different interactions on TREM2 function.

Introduction

Triggering receptor expressed on myeloid cells-2 (TREM2) is an extracellular innate immune receptor expressed on myeloid lineage cells such as dendritic cells (DCs) and resident tissue macrophages (including osteoclasts and microglia). The receptor consists of an extracellular V-type Ig domain followed by a short stalk (ectodomain = 19–172 aa), leading to a single transmembrane helix that interacts with DNAX-activation protein 12 (DAP12, also known as TYROBP) to mediate downstream signaling (Fig. 1a and b). TREM2 terminates with a short cytosolic tail (195–230 aa) lacking known signaling or trafficking motifs [1]. In addition to the membrane-bound form, soluble TREM2 (sTREM2) ectodomains can be generated by proteolytic processing that occurs within the protein stalk [2] or by alternative splicing [3] (Fig. 1b). The importance of TREM2 is highlighted by genetic studies linking TREM2 variants to various neurodegenerative diseases, including Alzheimer's disease (AD) [4,5]. TREM2 has been implicated in a wide array of functions including cell maturation, survival, proliferation, activation, phagocytosis, and the regulation of inflammation [1]. Accompanying this diverse set of functions is an even longer list of potential TREM2 ligands. Indeed, since its discovery, the identification of bona fide endogenous TREM2 ligands has proven elusive, although there is an emerging pattern of ligands that are anionic and/or lipidic in nature. It is unclear if the TREM2 ligand is among the suggested ligands or whether TREM2 is simply a highly promiscuous receptor that can engage a wide array of ligands. The goals of this review are to

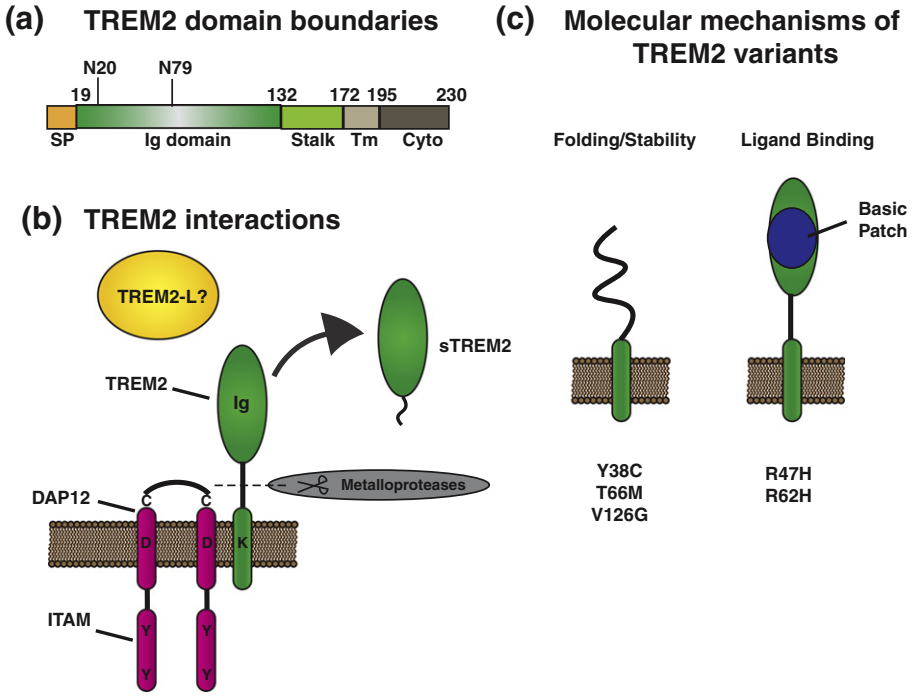

Fig. 1. Schematic for TREM2 domain boundaries and structure. (a) Schematic of TREM2 domain boundaries. SP = signaling peptide, Ig = immunoglobulin, Tm = transmembrane, and Cyto = cytosolic tail. N20 and N79 indicate the position of N-linked glycosylation sites. Numbers indicate domain boundaries. (b) Schematic representing TREM2 structure and interactions with DAP12. TREM2 is a single-pass transmembrane domain that interacts with DAP12 through polar interactions between transmembrane domains. TREM2 contains an Ig domain to interact with ligands. DAP12 exists as a disulfide-linked homodimer, and each monomer contains an ITAM motif. (c) Molecular impact of disease variants. Coding variants in the Ig domain of TREM2 have been found to impact either protein folding and stability (Y38C, T66M, V126G) or ligand binding (R47H, R62H). The major AD risk variants R47H and R62H impact binding to multiple ligands (Table 2) and are contained within a basic patch on the protein surface that likely mediates ligand binding.

(1) highlight functions for TREM2 evident from animal studies of homeostasis and disease, (2) identify facets of TREM2 signaling that may be influenced by different ligands, (3) discuss the evidence for the various TREM2 ligands, and (4) suggest where and how different ligands may be involved in TREM2 function. We develop the model that distinct ligands may mediate different components of TREM2 signaling and that a complex of ligands interacting with various portions of TREM2 may be required to assemble a productive signaling complex.

TREM2 in Disease

TREM2 variants are risk factors for neurodegenerative diseases

The importance of TREM2 in neuronal health was first demonstrated by genetic studies that identified *TREM2* variants in families with Nasu–Hakola disease (NHD, also known as polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy or PLOSL), a fatal disease characterized by presenile dementia and bone cysts [6–8]. NHD patients are homozygous for loss-of-function *DAP12* or *TREM2* variants. In some cases, *TREM2* mutant carriers present a fronto-temporal lobar form of dementia lacking the bone phenotype. The *TREM2* variants include splice site [7,9], early stop sites [7,10–12], and coding ectodomain mutations [7,8,13–15]. These mutations are all believed to produce nonfunctional proteins. More recently, separate coding variants in the Ig domain of TREM2 were linked to an increase risk for late onset AD (LOAD) [4,5]. The link between *TREM2* variants and LOAD, particularly the R47H and R62H variants, is now well-established [3,16–18]. *TREM2* AD risk variants are rare but carry roughly the same risk as a copy of the apolipoprotein E4 allele and clearly link the innate immune system to neurodegenerative disease [19]. Beyond AD, *TREM2* variants have been linked to other neurodegenerative diseases, including Parkinson's disease [20,21], sporadic amyotrophic lateral sclerosis [22], and fronto-temporal dementia [23,24], although these non-AD associations have not been as widely reproduced [16]. The association of distinct variants with different diseases