

REVIEW

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Microglial TYROBP/DAP12 in Alzheimer's disease: *Transduction of physiological and pathological signals across TREM2*

Jean-Vianney Haure-Mirande^{1†} , Mickael Audrain^{1†} , Michelle E. Ehrlich^{1,2,3*}  and Sam Gandy^{1,2,4,5*} 

Abstract

TYROBP (also known as DAP12 or KARAP) is a transmembrane adaptor protein initially described as a receptor-activating subunit component of natural killer (NK) cells. TYROBP is expressed in numerous cell types, including peripheral blood monocytes, macrophages, dendritic cells, and osteoclasts, but a key point of recent interest is related to the critical role played by TYROBP in the function of many receptors expressed on the plasma membrane of microglia. TYROBP is the downstream adaptor and putative signaling partner for several receptors implicated in Alzheimer's disease (AD), including SIRP1 β , CD33, CR3, and TREM2. TYROBP has received much of its current notoriety because of its importance in brain homeostasis by signal transduction across those receptors. In this review, we provide an overview of evidence indicating that the biology of TYROBP extends beyond its interaction with these four ligand-binding ecto-domain-intramembranous domain molecules. In addition to reviewing the structure and localization of TYROBP, we discuss our recent progress using mouse models of either cerebral amyloidosis or tauopathy that were engineered to be TYROBP-deficient or TYROBP-overexpressing. Remarkably, constitutively TYROBP-deficient mice provided a model of genetic resilience to either of the defining proteinopathies of AD. Learning behavior and synaptic electrophysiological function were preserved at normal physiological levels even in the face of robust cerebral amyloidosis (in *APP/PSEN1;Tyrobp*^{-/-} mice) or tauopathy (in *MAPT^{P301S};Tyrobp*^{-/-} mice). A fundamental underpinning of the functional synaptic dysfunction associated with each proteotype was an accumulation of complement C1q. TYROBP deficiency prevented C1q accumulation associated with either proteinopathy. Based on these data, we speculate that TYROBP plays a key role in the microglial sensome and the emergence of the disease-associated microglia (DAM) phenotype. TYROBP may also play a key role in the loss of markers of synaptic integrity (e.g., synaptophysin-like immunoreactivity) that has long been held to be the feature of human AD molecular neuropathology that most closely correlates with concurrent clinical cognitive function.

Keywords: Tyrobp/Dap12, Trem2, ApoE, miR-155, Disease-Associated Microglia (DAM), Sensome, Complement C1q, Alzheimer, Amyloid, Tau

Background

The proteinopathies and neuroimmune/neuroinflammatory features of Alzheimer's disease (AD) neuropathology underpin a major proportion of late-life cognitive failure. The AD-related proteinopathies include cerebral interstitial, cerebrovascular, and meningovascular deposition of amyloid- β (A β) peptides composed of 38-43 amino acid species that form unstructured oligomers and

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highly structured fibrils [1]. The full range of biological activities associated with these A β species remains to be fully elucidated. Recent evidence implicates some direct cytotoxic mechanisms wherein A β oligomers have been proposed to be more bioactive while A β fibrils have been proposed to be more inert. Evidence has recently developed independently from multiple labs and experimental systems that implicate interactions of A β oligomers with cell-surface prion protein (PrP), isotype 5 of the metabotropic glutamate receptor and/or intracellular protein kinases, e.g., PERK, Fyn, and cdk5 [2–4].

In addition to the possibility of direct neurotoxicity due to various A β -derived species, neuroinflammatory pathways can be driven not only by A β -derived oligomeric and fibrillar species but also by aggregates of microtubule-associated protein TAU (MAPT) that can assemble to form intracellular neurofibrillary tangles in neurons and/or glia. AD neuropathology includes not only amyloidosis and tauopathy, as many brains harboring AD neuropathology are also reported to contain Lewy body α -synuclein pathology [5, 6]. This property is apparent even among brains of subjects harboring autosomal dominant familial AD pathogenic mutations in *APP*, *PSEN1*, or *PSEN2* [7]. Each of these proteinopathies can influence each other and trigger and/or exacerbate immune-inflammatory events that almost always involve microglia, the central nervous system resident macrophages [8].

Microglia perform sentinel functions within the brain, regulating homeostasis and rapidly reacting to damage, infections and/or debris by adapting their phenotypes and phagocytic capacity. Despite their roles as “first responder” cells, the microglia arriving at the sites of AD-related proteinopathies can soon see their clean-up capacities outstripped, which, associated with the production of proinflammatory cytokines, can contribute to disease progression and neurodegeneration [9].

In addition to their phagocytosis-related duties, microglia support neurons by modulating neuronal activity [10] and by pruning synapses [11–13] especially during brain development [14, 15]. However, this process can be improperly activated during aging [16] and disease [17, 18]. Recent evidence demonstrates that oligomeric A β , in the company of C3, C1q, and apolipoprotein E (APOE), can drive pathological pruning that may play a role in how A β oligomers cause loss of synapses and lead to cognitive decline [19]. Another mechanism of A β oligomer-induced synapse loss may involve planar cell polarity (PCP) signaling components [20]. PCP signaling regulates synapse formation and maintenance during brain development [21], and recent evidence shows that binding of A β oligomers to PCP components is required for A β oligomer-induced synapse loss.

Blockage of PCP signaling using monoclonal antibodies decreases microglial activation, protects synapses from A β oligomer-induced loss, and preserves cognitive function [20]. Other evidence points to a type 1 interferon-related toxicity that degrades synaptic function and/or integrity [17]. However, the relationship(s) among oligomeric A β -C3-C1q-APOE* ϵ 4-related microglial synaptic pruning and type 1 interferon-related synaptic toxicity remain(s) to be clarified.

Research in the past few years has advanced our understanding of the molecular events underpinning the involvement of microglia in the etiology of neurodegenerative diseases. Genome-wide association studies (GWAS) have identified many AD-associated variants associated with microglia [22–24], and recent analyses revealed specific transcriptomic signatures for quiescent or “homeostatic” microglia when compared with disease-associated microglia (DAM) [25, 26]. Additionally, new approaches using human induced pluripotent stem cell-derived microglia [27], single-cell and single-nucleus RNA sequencing have contributed to our understanding of microglia in AD and AD-associated immune-inflammatory events. These observations support a formulation wherein microglia are not mere “spectators” during neurodegeneration but rather function as “initiators” and/or “active participants” in the progression of AD and neurodegenerative diseases.

GWAS-related approaches to human AD have identified candidate risk loci related to microglia in late-onset AD (LOAD). Two of the most studied are *APOE* and *TREM2* (for Tripping Receptor Expressed on Myeloid Cells 2). *TYROBP* (for tyrosine kinase binding protein; also known as *DAPI2* for DNAX activating protein-12 and as *KARAP* for killer cell-activating receptor-associated protein) is a transmembrane polypeptide that acts as an adaptor for several receptors on microglia and other myeloid cells. Interestingly, *TYROBP* forms a necessary bridge between *TREM2* at the microglial cell surface and *APOE* transcription within microglia. In 2013, Zhang et al. performed a multiscale gene network analysis combining neuropathology, whole-genome genotyping, and RNA-sequencing analyses, and identified *TYROBP* as a key network hub gene and driver in sporadic LOAD patients [28]. Concurrently, Hickman et al. (2013) identified a family of 100 transcripts highly enriched in microglia during a sensing activity and showed that *TYROBP* was a hub of this “sosome” [29]. Recently, our lab has confirmed in two mouse models of AD-related proteinopathies the critical events that can occur when *Tyrobp* gene expression is not optimized [30–33].

One explanation for this gene dose optimization requirement has been presented for outcomes when the inhibition of the tyrosine-protein kinase ABL has been

targeted to alleviate neurodegenerative diseases [34]. In this study, authors showed that broad inhibition of multiple tyrosine-protein kinases using low doses of inhibitors was more effective at reducing A β and tau toxicities and alleviating neurodegenerative pathologies than was ABL inhibition alone using more selective inhibitors [34]. Since TYROBP is a tyrosine kinase substrate phosphoprotein, this gene dose optimization phenomenon may be relevant not only for tyrosine kinases, but also for phospho-tyrosine-status-sensitive physiological effector substrates such as TYROBP.

Golde and colleagues have described another example of the requirement for empirical gene dose optimization studies [35]. In this example, they designed a protocol aimed at exploring the effect of the expression of the anti-inflammatory cytokine, interleukin-10 (IL-10), on A β pathology in the brains of two mouse models of amyloid pathology (TgCRND8 and Tg2576). In contrast to several reports demonstrating that proinflammatory cytokines promote amyloid pathology [36–38], IL-10 expression increased A β accumulation, decreased synaptic markers, and impaired learning behavior in the *APP* mice. Interestingly, transcriptomic analyses revealed increased APOE mRNA levels in mice expressing IL-10 that were associated with increased APOE protein levels within the plaque-associated insoluble cellular fraction. These observations suggest that proinflammatory and anti-inflammatory signals can negatively affect amyloid pathology and cognition and demonstrate the complex interplay between innate immunity and proteostasis in neurodegenerative diseases, an interaction that Golde and colleagues have named “immunoproteostasis” [35]. Given the complex role that TYROBP plays in integrating the interrelationships linking environmental sensing, signal transduction, and phagocytosis, the term “immunoproteostasis” might well apply to TYROBP gene expression manipulation in our hands in much the same way that IL-10 manipulation yielded unexpected results in the hands of Golde and colleagues [35].

In this review, we introduce the structure and signaling of TYROBP and present an overview of its roles in the brain. We discuss the most notable advances on the role of TYROBP in AD pathogenesis. Specifically, we summarize our previous reports investigating the possibility that modulation of TYROBP levels or activity might play a role in cognitive resilience. In particular, we outline our observations demonstrating that TYROBP deficiency in mouse models of AD-related proteinopathies sustains normal learning behavior and electrophysiological functions even in the face of robust amyloidosis or tauopathy and that TYROBP pathways may act, at least in part, via complement-mediated and/or ERK-related pathways. Because of these data and others, we suggest

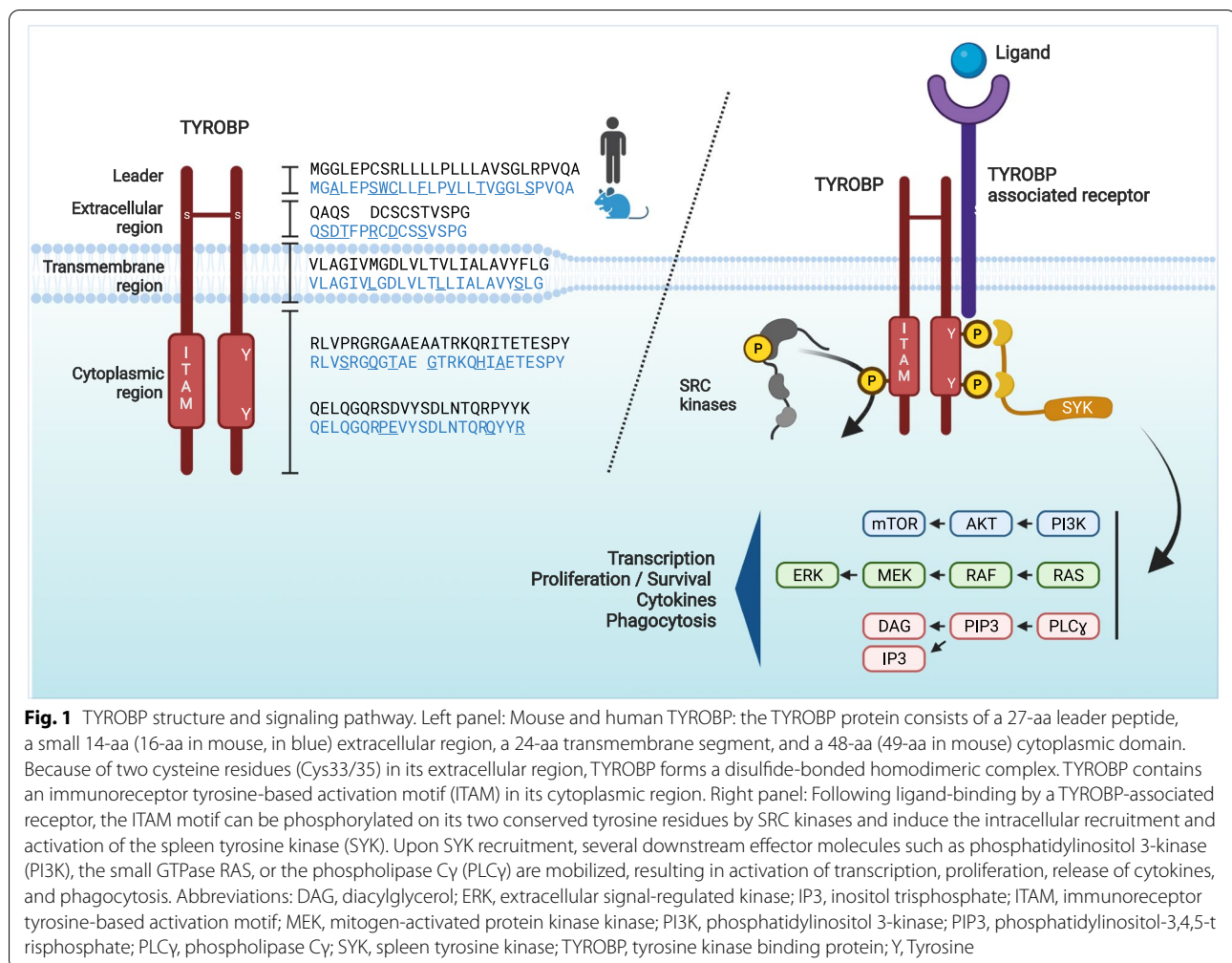
that the microglial sensome is not the exclusive province of TREM2.

TYROBP structure and signaling

Initially described in NK cells as KARAP [39–41], TYROBP is expressed in peripheral tissues in multiple lymphoid and myeloid cell subtypes, including osteoclasts. In the brain, TYROBP is mostly expressed in microglia but also in dendritic cells. The human *TYROBP* gene is located on chromosome 19 (7 in mouse) and encodes a 113 (114 in mouse) amino acid (aa) type I transmembrane adapter protein (Fig. 1). The TYROBP protein consists of a 27-aa leader peptide, a small 14-aa (16-aa in mouse) extracellular region, a 24-aa transmembrane segment, and a 48-aa (49-aa in mouse) cytoplasmic domain. Because of two cysteine residues (Cys33/35) in its extracellular region, TYROBP forms a disulfide-bond-crosslinked homodimeric protein. TYROBP contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic region. This ITAM motif is the only signaling domain identified for TYROBP and can be phosphorylated by SRC on one or both of two highly conserved tyrosine residues. The characterization of the differential protein-protein interactions between the spleen tyrosine kinase (SYK) and mono- vs. di-phosphorylated ITAM tyrosyl residues of TYROBP is an area of ongoing interest (https://ftp.www.pdb.org/pub/pdb/validation_reports/q5/7q5w/7q5w_full_validation.pdf.gz). The tyrosyl phosphorylated form of TYROBP [42] induces the intracellular recruitment and activation of protein kinases, including the spleen tyrosine kinase (SYK) in myeloid cells and SYK and ZAP70 in NK cells. Upon SYK recruitment, several downstream effector molecules, including phosphatidylinositol 3-kinase (PI3K), the small GTPase RAS, and/or the phospholipase C γ (PLC γ) are mobilized.

As is the case for many immune system receptors, TYROBP is part of a multi-subunit protein complex in which the recognition of a specific ligand and the downstream intracellular signaling domain are the product of distinct subunits. Multi-protein complexes involving TYROBP and various receptor ectodomains-intramembranous domains are formed through a complex electrostatic network involving the hydrophilic intramembranous domain residues [43, 44]. Ligation of TYROBP-associated receptors to TYROBP provides docking sites for various ligands that can initiate intracellular signals through TYROBP and its ITAM motif.

Most of these pathways trigger microglial activation with increased release of cytokines (such as IL-1, IL-6, or TNF α), cytoskeletal rearrangement, and phagocytosis. However, it has been reported that TYROBP can also inhibit phagocytosis [45–48]. To explain how some



TYROBP-associated receptors promote activation signals while others amplify cellular inhibition, Turnbull and Colonna (2007) proposed an avidity-based model [49]. Thus, while a high-avidity interaction between a ligand and a TYROBP-associated receptor would induce a complete phosphorylation of TYROBP in the ITAM motif and the recruitment of SYK, a low-avidity interaction would induce an incomplete phosphorylation of TYROBP and the activation of the inhibitory phosphatase SH2-domain-containing protein tyrosine phosphatase 1 (SHP-1, encoded by *PTPN6*), leading to the induction of inhibitory signaling [49].

TYROBP receptors in the brain

Many receptors have been identified that act by furnishing ligand-binding ectodomains and short transmembrane domains to the TYROBP adaptor [49–51], and some of these receptors are expressed in human and rodent brains and are known to be associated with AD (Table 1). For example, the signal regulatory protein- β 1

(SIRP β 1) is a microglial receptor associated with TYROBP [52, 53]. SIRP β 1 expression is increased in the brains of patients and animal models of AD pathology, and this molecule was previously linked to the phagocytosis and clearance of debris and A β aggregates [55]. However, the natural ligand for SIRP β is unknown.

The TYROBP receptor that has received the most attention in the AD field is TREM2 because of the discovery in 2013 that patients harboring the *TREM2*^{R47H} variant are at increased relative risk for developing AD similar to that associated with the APOE* ϵ 4 allele [97, 98]. Heretofore, APOE* ϵ 4 had been anticipated to be the most potent genetic factor that was likely to exist for enhancing the relative risk for AD. Additional rare variants of *TREM2* have been discovered (e.g., R62H, T96K, D87N), and, for the most part, these variants are shown or are predicted to confer a loss of function of TREM2 by decreasing the ligand-binding capacity or cell surface expression. The TREM2 extracellular domain is the receptor part of the protein that binds many ligands,

Table 1 Microglial and myeloid cell-surface receptors associated with TYROBP

Receptors	Gene	Species	Ligands	Ref.	Implication for disease	Ref.
SIRPB1	<i>SIRPB1</i>	Human, mouse	Unknown	[52–54]	Increased expression in AD	[55]
TREM1	<i>TREM1</i>	Human, mouse	PGLYRP1, HMGB1, HSP70, extracellular actin	[56–59]	Septic shock, pneumonia, bacterial infectious diseases	[60–62]
TREM2	<i>TREM2</i>	Human, mouse	ApoE, A β oligomers, phospholipids, lipopolysaccharide	[63–66]	Nasu-Hakola disease, early-onset AD, FTD	[67–69]
TREM3	<i>Trem3</i>	Mouse	Unknown	[70]	Unknown	
TREM5	<i>CD300LB</i>	Human, mouse	Unknown	[71]	Unknown	
MDL1 (CLEC5a)	<i>MDL1</i>	Human, mouse	Fucose and mannose, membrane glycans, hemagglutinin protein of influenza viruses	[72–74]	Chronic obstructive pulmonary disease, viral infections	[74, 75]
SIGLEC-14	<i>SIGLEC14</i>	Human	Glycans	[76, 77]	Unknown	
SIGLEC-15	<i>SIGLEC15</i>	Human, mouse	Glycans, tumor-associated glycan structure, CD44	[78, 79]	Osteopetrosis	[80]
SIGLEC-16	<i>SIGLEC16</i>	Human, mouse	Glycans	[81]	Unknown	
SIGLEC-H	<i>SiglecH</i>	Mouse	Unknown	[82, 83]	Unknown	
pDC-TREM	<i>pDC-Trem</i>	Mouse	Unknown	[84]	Unknown	
PILRB	<i>PILRB</i>	Human, mouse	Sialylated O-linked sugars	[85–88]	Unknown	
mCD33 (SIGLEC-3)*	<i>Siglec3</i>	Mouse	Glycans	[82]	Polymorphisms of human CD33 linked to AD	[89–91]
IREM2	<i>CD300E</i>	Human, mouse	Unknown	[92, 93]	Unknown	
MAIR-II (LMIR2, CLM-4, DigR1)	<i>Cd300C2</i>	Mouse	Unknown	[94–96]	Unknown	

AD Alzheimer's disease, ApoE Apolipoprotein E, A β Amyloid- β , CD300LB CD300-Like Family Member B, CLEC5 C-Type Lectin Domain Containing 5A, Siglec Sialic Acid-Binding Immunoglobulin-Type Lectins, FTD Frontotemporal dementia, mCD33 Mouse CD33, MAIR-II Myeloid-associated immunoglobulin-like receptor, pDC-TREM Plasmacytoid Dendritic Cells-Triggering Receptor Expressed On Myeloid Cells, SIGLEC-14 Sialic Acid Binding Ig-Like Lectin 14, SIGLEC-15 Sialic Acid Binding Ig-Like Lectin 15, SIGLEC-16 Sialic Acid Binding Ig-Like Lectin 16, SIGLEC-H Sialic Acid Binding Ig-Like Lectin H, SIRPB1 Signal Regulatory Protein-B1, TREM1 Triggering Receptor Expressed On Myeloid Cells 1, TREM2 Triggering Receptor Expressed On Myeloid Cells 2, TREM3 Triggering Receptor Expressed On Myeloid Cells 3, TREM5 Triggering Receptor Expressed On Myeloid Cells 5, TYROBP Tyrosine Kinase Binding Protein, *mCD33: mouse CD33, based on the sequence similarity in the transmembrane domain with that of mouse SIGLEC-H

including phospholipids, A β oligomers, DNA, and bacterial lipopolysaccharide. Interestingly, several apolipoproteins, including APOE, bind to TREM2 and this binding is abolished or reduced in the presence of TREM2 disease variants [63, 64, 99]. Because of the absence of signaling motifs in the TREM2 intracellular domain, full-length TREM2 almost certainly exerts its actions via TYROBP. The long extracellular ectodomain can also be cleaved by proteases such as ADAM10, ADAM17, or meprin β , liberating soluble TREM2 (sTREM2). sTREM2 has been shown to be biologically active in enhancing the production of inflammatory cytokines and microglia survival [100], binding oligomeric A β [101], and blocking A β oligomerization and fibrillization [102]. Several studies also reported that sTREM2 was positively correlated with cerebrospinal fluid (CSF) levels of phosphorylated TAU [103, 104]. Although oligomeric A β can induce sTREM2 shedding and viral infections such as HIV increased levels of sTREM2 in the CSF, conditions that modulate sTREM2 shedding from full-length TREM2 are not fully understood [102, 105] and may occur to block the activity of full-length TREM2 and its downstream signaling. Also, by binding similar ligands, sTREM2 and full-length

TREM2 may share some biological functions that do not involve interaction with TYROBP. More experiments aimed at deciphering the precise role of sTREM2 and full-length TREM2/TYROBP complex in AD are needed.

Other TREM receptors present on the myeloid cells, such as TREM1, TREM3, and TREM5, can associate with TYROBP. Of note, while a low level of TREM3 is detected in mouse microglia, TREM3 in humans is present as a pseudogene [56, 70, 106]. Although like most TYROBP-associated receptors, their ligands are unknown and their roles in brain biology are not fully understood, TREM1 has been implicated in septic shock and bacterial infectious diseases [60–62] demonstrating the role of TYROBP-associated receptors in the immune response against bacterial infections.

CLEC5a (or MDL1) is a member of the C-type lectin/C-type lectin-like domain superfamily and has been shown to interact with TYROBP [72]. Ligands of CLEC5a include the fucose and mannose sugars of the dengue virus and the hemagglutinin protein of influenza viruses [73, 74]. These data further support the role of the TYROBP pathway in the immune response against pathogens.

Members of the sialic acid-binding immunoglobulin-type lectins (Siglec) proteins comprise another class of receptors that associates with TYROBP. Siglecs are mainly expressed in immune cells and recognize glycans in sialic acid. The Siglec family contains 15 members in humans and 8 members in mice. Siglecs are rapidly evolving genes and are partially conserved across species. The majority of the Siglecs contain intracellular Immunoreceptor Tyrosine-based Inhibitory Motifs (ITIMs) and recruit the inhibitory phosphatase SHP-1, leading to the induction of inhibitory intracellular signaling. Still, some Siglecs have a positive amino acid charge (lysine or arginine residues) in the transmembrane domain and can associate with TYROBP and transduce signals through ITAM motifs (Siglec-14, -15, -16) [76–78]. However, human RNAseq data from purified cell types suggest a relatively low expression level in microglia, with Siglec-14 being expressed at a higher level than Siglec-15 and -16 (<http://www.brainrnaseq.org>). The precise roles of these Siglecs in the brain and microglia remain to be investigated. A mouse-specific Siglec (Siglec-H) was the first Siglec to be reported to associate with TYROBP [82]. Siglec-H is expressed in dendritic cells, macrophages, and microglia [83, 107]. Although the mechanism is not fully understood, the activation of TYROBP signaling by Siglec-H inhibits the production of type I interferon (IFN) [108]. Further elucidation of this link involving TYROBP and Siglec-H may converge with type I IFN signaling in causing or exacerbating synaptic dysfunction and degeneration in AD [17].

CD33 (also known as Siglec-3) was identified as a top-ranked AD risk factor by GWAS [89]. Elevated levels of CD33 protein were reported in AD brain and were associated with amyloid pathology and disease progression [90, 109]. Moreover, de Jager and colleagues reported a positive correlation of CD33 protein level with that of TREM2 in humans. The mouse and human CD33 are substantially different proteins in expression patterns and ligand recognition [110]. Notably, unlike human CD33 which contains two ITIM motifs and associates with SHP-1 [111–113], mouse CD33 lacks one of the ITIM motifs and is suggested to interact with, and signal through, TYROBP [82]. In *APP/PSEN1* mice, the absence of CD33 decreased the brain levels of A β 42 and amyloid plaque burden [91], suggesting a negative role of CD33 in amyloid uptake by microglia. Of note, we observed a downregulation of *Cd33* and *Trem2* in the brains of *APP/PSEN1* mice in the absence of TYROBP [33]. Although mouse and human CD33 studies may not be directly comparable due to sequence dissimilarities and signaling, our results dovetail with

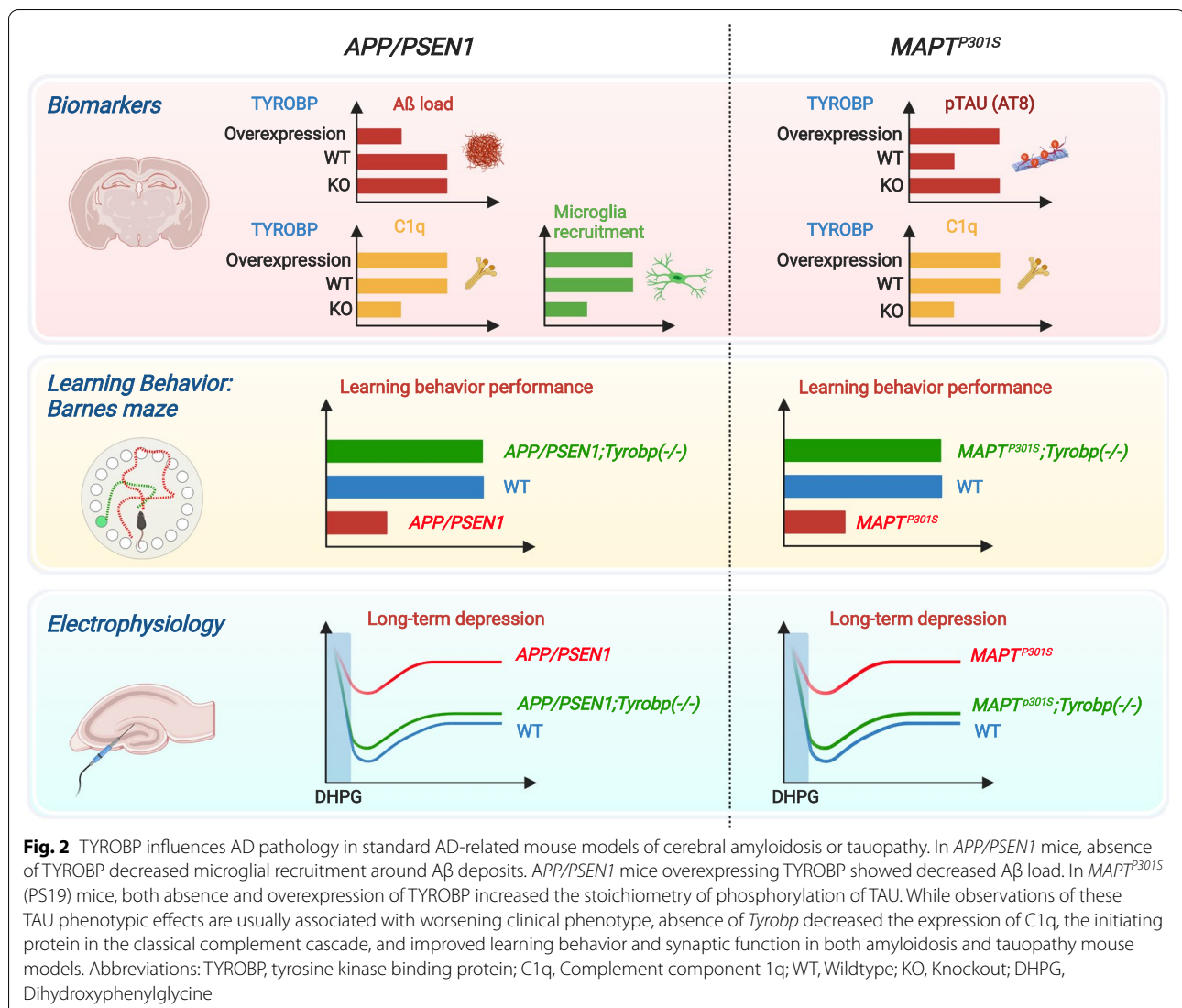
those of de Jager and colleagues and suggest regulation of *Cd33* and *Trem2* expression by TYROBP.

TYROBP in Alzheimer's disease and mouse models of cerebral amyloidosis or tauopathy

Since 2013 and the identification by Zhang and colleagues of *TYROBP* as a key network driver in sporadic LOAD [28], several reports have confirmed the crucial involvement of TYROBP in AD pathology and progression. TYROBP expression is increased in AD patients and AD mouse models [28, 114], and rare *TYROBP* missense coding variants have been identified in patients with familial early-onset AD [115]. Moreover, as discussed above, TYROBP acts as a downstream adaptor for microglial receptors known to interact with A β . Finally, deletion and premature termination, loss-of-function mutations in the *TYROBP* gene are associated with Nasu-Hakola disease, a rare recessively-inherited disease associated with early-onset dementia [116].

Our lab characterized the in vivo consequences of TYROBP deficiency in standard AD-related mouse models of cerebral amyloidosis or tauopathy. Although in our hands the absence of TYROBP did not affect the total number of microglia in the cortex and hippocampus of WT or AD-related mouse models as compared to mice with WT level of TYROBP, we showed that a constitutive deficiency of TYROBP in the *APP/PSEN1* mice, a mouse model of the cerebral amyloidosis of AD, reduced the clustering of microglia around A β plaques. Interestingly, *APP/PSEN1* mice deficient for TYROBP maintained normal learning behavior assays and electrophysiology recordings at both 4 and 8 months of age (Fig. 2). In these same TYROBP-deficient, *APP/PSEN1* mice, we observed a dramatic reduction of most of the *Tyrobp*-driven complement subnetwork, as previously observed from human brain RNA sequencing [28, 32, 33]. We also observed repression of the induction of genes involved in the switch from homeostatic microglia to DAM, including *Trem2*, *Clec7a*, and *Cst7* (Fig. 3). In addition, the absence of TYROBP in the *APP/PSEN1* mice decreased the expression of *Irf8*, a transcription factor implicated in microglia development, regulation of proinflammatory cytokine expression, and recently involved in microglial migration and microglial spread of A β [117–119].

When crossed with the PS19 tauopathy mouse model (*MAPT^{P301S}*), mice with a *Tyrobp* deletion showed evidence for an increased stoichiometry of phosphorylation of TAU as well as enhanced transneuronal diffusion of TAU. These observations were confirmed in *Tyrobp*^{-/-} mice injected with AAV-TAU [31]. Despite these phenotypic effects usually associated with worsening clinical phenotype, *MAPT^{P301S}* mice deficient for TYROBP showed improved learning behavior



and synaptic function, similar to what we observed in *APP/PSEN1* mice (Fig. 2) [31, 32]. Interestingly, one common molecular property shared between *APP/PSEN1;Tyrobp^{-/-}* and *MAPT^{P301S};Tyrobp^{-/-}* mice was the reduction of the level of complement protein C1q, suggesting that deletion of TYROBP drives beneficial effects in learning behavior and synaptic functions in part via decreased C1q levels [31, 32] (Fig. 2).

Recently, we interrogated the consequences of TYROBP upregulation in microglia. We developed a novel transgenic mouse overexpressing TYROBP and crossed it with *APP/PSEN1* and *PS19* mice [30]. Similar to TYROBP deficiency in the setting of our studies, TYROBP overexpression did not affect the total number of microglia in the brain. We reported a decrease of brain amyloid burden in the *APP/PSEN1* mice overexpressing TYROBP and an increase of TAU phosphorylation

stoichiometry in the *MAPT^{P301S}* mice overexpressing TYROBP, surprisingly similar to results obtained in the *MAPT^{P301S};Tyrobp^{-/-}* mice [31]. These data confirm the crucial role of microglia and TYROBP in both amyloidosis and tauopathy progression (Fig. 2) and the complex interplay between innate immunity and proteostasis in neurodegenerative diseases [37].

TYROBP and the complement system

The complement system was initially described in the periphery and consists of multiple proteins in a cascade that enhances the immune system to react to microbes, pathogens, or other damaging agents. The system performs analogous functions in the brain with the clearance of damaged cells, unwanted cellular materials, and even synapses [11, 12]. Synaptic pruning is a physiological process described initially during the development

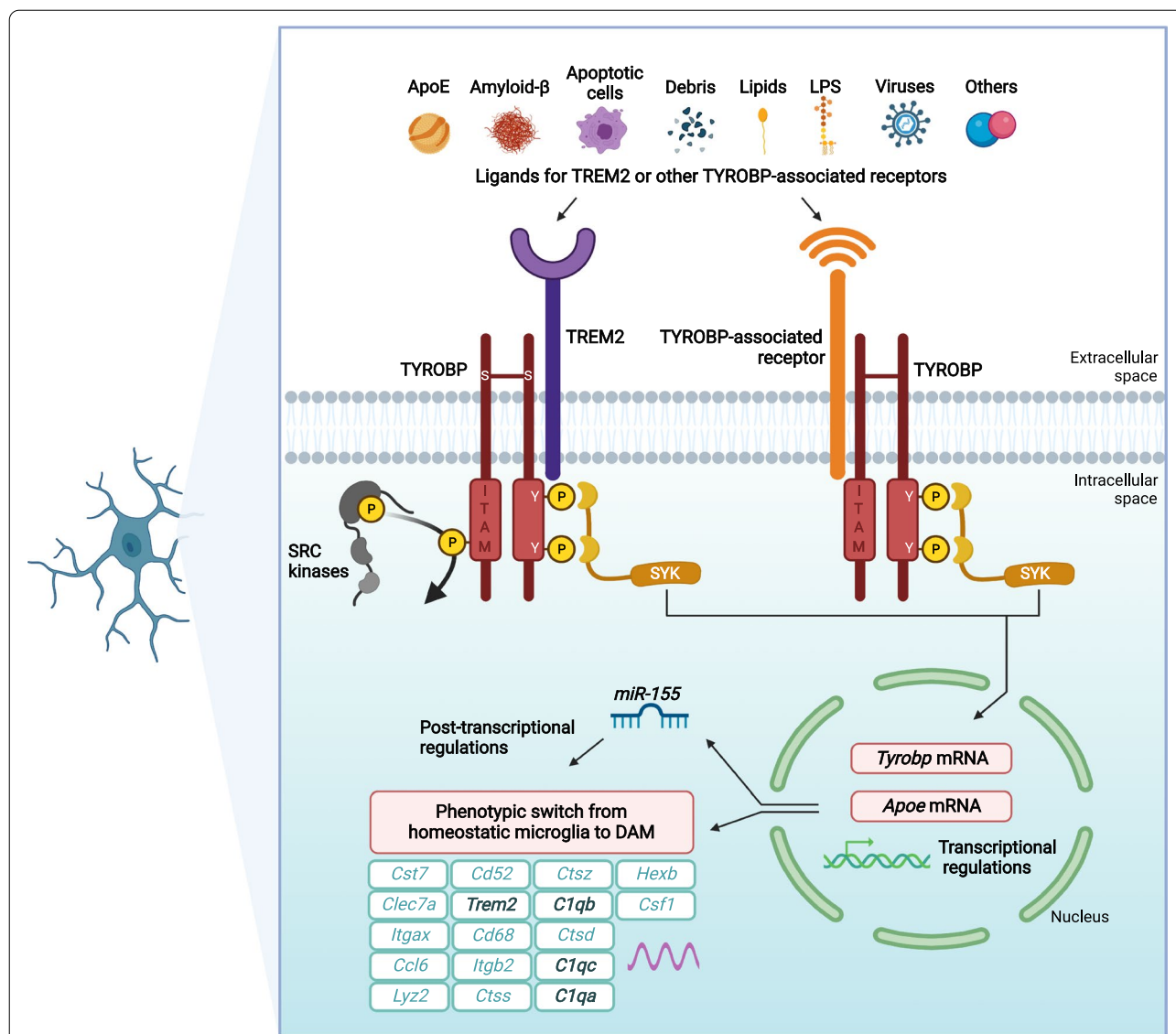


Fig. 3 Probable ligand-induced TYROBP signaling in recruited microglia. Ligand-induced TYROBP signaling is initiated by apolipoprotein E, A β , debris, or other currently unidentified ligands at sensing receptors and leads to phosphorylation of the tyrosine residues in the cytoplasmic ITAM of TYROBP by SRC kinases and the recruitment of SYK. In turn, SYK signaling can increase transcription of *Tyrobp* and *ApoE*. This series of events forms the basis for the phenotypic switch from homeostatic microglia to DAM and may be in part post-transcriptionally regulated by *miR-155*. We speculate that in mice lacking *Trem2*, recruited microglia cause other receptor ectodomains to acquire sensing capability either because these receptors always signal by complexing with TYROBP, or because signals across other complexes are induced as a compensatory mechanism due to the absence of *Trem2*. Abbreviations: APOE, apolipoprotein E; C1q, complement protein C1q; Ccl6, C-C motif chemokine ligand 6; Cd52, CD52 molecule; Cd68, CD68 molecule; Clec7a, C-Type lectin domain containing 7A; Csf1, colony stimulating factor 1; Cst7, cystatin F; Ctsd, cathepsin D; Ctss, cathepsin S; Ctsz, cathepsin Z; DAM, disease-associated microglia; Hexb, hexosaminidase subunit beta; Itgax, integrin subunit alpha X; Itgb2, integrin subunit beta 2; Lyz2, lysozyme 2; miR-155, microRNA-155; SYK, spleen tyrosine kinase; TREM2, triggering receptor expressed on myeloid cells-2; TYROBP, tyrosine kinase binding protein; Y, tyrosine. Adapted and reprinted with permission from Wiley Publishing, Hoboken, NJ

to eliminate weaker synapses to the advantage of more robust and more active synapses. Still, recent studies show that the process can be inappropriately activated during aging [16] and AD [17, 18]. C1q, the initiating protein in the classical complement cascade, is mainly

produced by microglia in the brain [120] and is also part of the complement subnetwork driven by TYROBP [28]. Both TYROBP and C1q were recently identified as key predictors of gastric cancers [121], supporting a strong link between these two proteins even beyond AD. C1q is

upregulated in amyloidosis and tauopathy mouse models [32, 114, 122] and, as described above, our team observed that a deficiency of TYROBP induces a dramatic reduction of C1q in both *APP/PSEN1* and *MAPT^{P301S}* mice (Fig. 2) [31, 32]. This decrease is associated with the maintenance of normal learning behavior and electrophysiological properties, supporting suggestions from others that C1q is a target of interest in the treatment of neurodegenerative diseases [11, 18]. TYROBP and C1q transcripts are upregulated in close proximity to amyloid plaques in the human AD brain, while TREM2 transcripts are not closely approximated to plaques [114]. This seems to confirm that microglia sense plaques and respond by activating the complement cascade through the release of C1q, apparently recognizing the plaque as a “foreign” conformation despite its origin from a proteolytically processed “self” holoprotein, human APP. The tagging of neurons by C1q may be a trigger leading to neuronal dystrophy, tau phosphorylation, and neurodegeneration.

TYROBP: A hub for phagocytosis signaling pathways?

As previously mentioned, TYROBP interacts closely with receptors involved in phagocytosis, and a substantial body of evidence indicates that several key receptors involved in amyloid clearance or compaction are closely linked to TYROBP. In preparation for phagocytosis, a respiratory burst generates reactive oxygen species and involves an interaction between TYROBP and complement receptor 3 (CR3). CR3 is a heterodimer consisting of the integrins CD11b and CD18, and is an important TYROBP-related receptor in microglia. While the direct binding between TYROBP and CD11b/CD18 is still debated, several reports have demonstrated that TYROBP is required for signaling downstream of CR3. Syk and the ITAM of TYROBP are, for example, required for integrin signaling in neutrophils and macrophages [123, 124]. Additionally, CD11b acts through TYROBP in microglia-mediated neuronal apoptosis during development [125]. Notably, in the current discussion, blocking CR3 signaling -- if initiated before the accumulation of AD-related cerebral amyloidosis -- can protect synapses in the brains of mouse models from that component of AD pathology [126]. Our reports suggest a direct regulation of CR3 by TYROBP which may mediate, at least in part, the beneficial effects of TYROBP deletion on learning behavior and synaptic functions. Thus, we showed that *APP/PSEN1* mice deficient for TYROBP displayed decreased expression of *Itgam* encoding for CD11b (RNAseq, adj *p*-value=0.02) [32]. On the other hand, *MAPT^{P301S}* mice overexpressing TYROBP displayed a

trend toward increased *Itgam* (qPCR, *p*-value=0.12) (Audrain et al., unpublished data).

Recently, Huang et al. (2021) highlighted the role of TAM receptors AXL and MER in amyloid plaque construction by microglia in *APP/PSEN1* mice [127]. They showed that AXL and MER detect and react to amyloid plaques and that deletion of either of these genes blocks phagocytosis and “organization” of the plaques by microglia [127]. We observed a similar phenotype in the *APP/PSEN1* mice deficient for TYROBP [32, 33]. *Axl* transcripts were decreased (RNAseq, adj *p*-value=0.27, *p*-value=0.004) in 8 month-old *APP/PSEN1;Tyrobp^{-/-}* vs. *APP/PSEN1* [32], but were increased in 4 month-old *APP/PSEN1* mice overexpressing TYROBP vs. *APP/PSEN1* (qPCR, *p*-value=0.0092) [30]. Further investigation is required to understand the complex interrelationships that underpin these various receptors and adaptors and their actions in the orchestration of phagocytosis.

TYROBP, sensome, and microglial switching

Microglia constantly monitor the brain environment, and many alterations of brain homeostasis can induce a microglial response. Several transcriptomic studies describe distinct signatures for microglia that define their states from healthy to disease-associated. These transcriptomic profiles are essential to an elucidation of which genes and proteins are required to trigger specific responses depending on the alterations faced by microglia and the surrounding cells with which they communicate. Using single-cell sequencing in *5xFAD* mice, Keren-Shaul et al. (2017) showed a unique subtype of microglia, referred to as Disease-Associated Microglia (DAM), localized near the amyloid plaques [26]. Using *Trem2^{-/-}* mice, they identified two sequential but distinct stages in the switch to a DAM phenotype. The first step is *Trem2*-independent and requires the activation of genes that include *Tyrobp* and *ApoE*. The second step was found to be *Trem2*-dependent and associated with phagocytosis. A report published by Krasemann et al. (2017) identified a similar signature in microglia acquiring a neurodegeneration-associated phenotype (MGnD) in models of amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and AD, and pointed to microRNA-155 (*miR-155*) as an effector of the MGnD phenotype [25]. This study and a report from Butovsky et al. [128] showed that ablation of *Trem2*, *ApoE*, or *miR-155* locks microglia into a homeostatic state blocking the formation of MGnD. Of note, our recent reports placed *miR-155* at the intersection of a multiplex of AD pathogenic components involving innate immunity, viral response, synaptic physiology, and pro-amyloidogenic pathways [129]. Although similar, the study by Krasemann et al. (2017) contrasts with Keren-Shaul et al. (2017), in which *ApoE*

upregulation appeared to be independent of *Trem2*. More recently, Chen et al. (2020) used a combination of spatial transcriptomics and in situ sequencing to avoid one of the main drawbacks of these types of analyses, i.e., averaging the transcriptomes between microglia which are and are not recruited around the amyloid plaques [114]. They investigated the transcriptional changes occurring in a 100 μm diameter around the amyloid plaques of *APP^{NL-G-F}* mice and defined a plaque-induced gene (PIG) network of 57 genes in which *Trem2*, *Tyrobp*, *ApoE*, and other complement-related genes were among the upregulated genes. When performed in human AD brain slices, both *Tyrobp* and *ApoE* transcripts were confirmed as enriched, but, unexpectedly, *Trem2* was not among the human PIGs. As stated above, our lab showed that the absence of *Tyrobp* in *APP/PSEN1;Tyrobp^{-/-}* mice represses the induction of many genes involved in this DAM switch, including *Trem2*, complement (*C1qa*, *C1qb*, *C1qc*, and *Itgax*), *Clec7a* and *Cst7* (Fig. 3) [32]. Furthermore, we recently provided evidence that concurrent upregulation in microglia of both *Tyrobp* and *ApoE* is interconnected during microglial sensing of amyloid deposits and that these events take place independent of *Trem2* but are dependent on *Tyrobp* (Fig. 3) [30]. The damage-associated signatures described in all DAM, MGnD, and PIG microglia suggest that microglial transition from a homeostatic to a disease-associated state is choreographed by multiple components and involves TREM2, TYROBP, and APOE. Our data confirmed the two stages described by Keren-Shaul et al. (2017), in which the first stage would eventually correspond to a sensing of the amyloid plaques by the microglia and where both *Tyrobp* and *ApoE* are upregulated. The first stage is independent of *Trem2* and would be followed by a second stage that is dependent on *Trem2* and mostly associated with phagocytosis.

Link between Nasu-Hakola and Alzheimer's diseases?

Nasu-Hakola disease, also known as polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOS), is characterized by multiple bone cysts and progressive presenile dementia. This rare disease was first described in 1973 [130, 131], and most patients have been identified in Japan and Finland. PLOS is caused by autosomal recessive deletion or premature termination loss of function mutations in either *TREM2* or *TYROBP* [116]. This appears to distinguish PLOS mutations in *TREM2* or *TYROBP* from the missense mutations that associate TYROBP with AD [115]. TYROBP and TREM2 are expressed in most innate immune and myeloid cells, including osteoclasts. By differentiating peripheral blood mononuclear cells isolated from Nasu-Hakola patients,

Paloneva et al. (2000) showed that loss of function mutations in both *TREM2* and *TYROBP* induced a delayed and sub-optimal differentiation of osteoclasts associated with bone resorption [116]. The neurological stage of the disease is clinically similar to a frontal lobe syndrome and frontotemporal dementia (FTD), and FTD can be difficult to distinguish clinically from AD. Although *TREM2* and *TYROBP* mutations are causative for Nasu-Hakola disease and increase the risk of AD, the link between these two dementias is still unclear. A β deposits have been observed in the cortex of a 39-year-old woman with the *TREM2* Q33X mutation and Nasu-Hakola disease [132]. However, Satoh et al. (2018) studied the expression of A β in five Nasu-Hakola cases and concluded that amyloid plaques were almost undetectable in these brains [133]. Interestingly, other studies revealed that TREM2/TYROBP interacts closely with the colony-stimulating factor 1 receptor (CSF1R) [123, 134]. Strikingly, there is a CSF1R mutation that causes white matter disease with dementia termed hereditary diffuse leukoencephalopathy with spheroids (HDLS) [135]. Thus, both Nasu-Hakola and HDLS could involve similar or identical microglial pathway(s). Further studies in large populations will be essential to evaluate whether associations exist between TYROBP and other dementias.

Concluding remarks

Microglial biology and pathobiology have converged to create a highly active research area in AD and other neurodegenerative diseases. The rate of publication of microglia-related papers per year has tripled over the past decade. However, the range of microglial actions and their abilities to worsen or attenuate AD makes microglia-oriented interventions still uncertain. Specifically, whether microglia should be inhibited or activated, and when in the course of clinical or preclinical AD microglia can be targeted effectively, are all key pieces of information that currently remain unknown [136]. TREM2 has provided a valuable object lesson since many investigators proposed that upregulating TREM2 would be beneficial since AD-associated variants specify loss of function [137]. Interestingly, a recent antisense oligonucleotide (ASO) strategy showed that acute reduction of *Trem2* in *APP/PSEN1* mice decreases amyloid deposition by increasing microglial phagocytosis [138]. This confirms our recent report showing that, even in the absence of *Trem2*, microglia can still sense the presence of amyloid plaques [30].

Furthermore, many additional microglial receptors interacting directly and indirectly with TYROBP are involved in AD pathogenesis. TYROBP is one of the two main ITAM-containing adaptors that mediate signaling by heterologous receptors [139]. This suggests that

various extracellular stimuli — acting through TREM2, Toll-like receptors, and other receptors — can lead to activation of intracellular signaling pathways, suggesting that altering the activity of a single microglial signaling pathway may not be sufficient for full activation.

The association of TYROBP with sporadic and early-onset AD and its role as a key regulator for many AD-associated functions of microglia, including phagocytosis, complement activation, synaptic pruning, and a switch from homeostatic to DAM state, suggest that the modulation of TYROBP level or activity may represent a therapeutic opportunity in AD. Although the potential “druggability” of microglial receptors and adapters such as TYROBP may present challenges due to the interactions of each with numerous ligands and signaling pathways, the recent discovery of CNS-penetrating small molecules like sobetirome and Sob-AM2, two thymimetic agents capable of targeting TREM2, may ultimately lead to a viable therapeutic approach to selective manipulation of individual microglial events [140]. Overall, a better understanding of TYROBP and its many interactors and pathways will improve our understanding of the role(s) played by microglia in the etiology and pathogenesis of human neurodegenerative diseases.

Abbreviations

AD: Alzheimer's disease; ALS: Amyotrophic Lateral Sclerosis; ApoE: Apolipoprotein E; ASO: Antisense Oligonucleotide; A β : Amyloid- β ; CD300LB: CD300-Like Family Member B; CLEC5: C-Type Lectin Domain Containing 5A; CSF: Cerebrospinal Fluid; Siglec: Sialic Acid-Binding Immunoglobulin-Type Lectins; CSF1R: Colony-Stimulating Factor 1 Receptor; DAM: Disease-Associated Microglia; DAP12: DNAX Activating Protein-12; ERK: Extracellular Signal-Regulated Protein Kinase; FTD: Frontotemporal Dementia; GWAS: Genome-Wide Association Studies; HDLS: Hereditary Diffuse Leukoencephalopathy with Spheroids; IFN: Type I Interferon; IL-12/23: Interleukin-12/23; ITAM: Immunoreceptor Tyrosine-Based Activation Motif; ITIM: Immunoreceptor Tyrosine-Based Inhibitory Motifs; KARAP: Killer Cell-Activating Receptor-Associated Protein; LOAD: Late-Onset AD; MAPT: Microtubule-Associated Protein TAU; mCD33: Mouse CD33; MGnD: Microglial Neurodegenerative Phenotype; miR-155: microRNA-155; MS: Multiple Sclerosis; MAIR-II: Myeloid-associated immunoglobulin-like receptor; NK Cells: Natural Killer Cells; PCP: Planar Cell Polarity; PI3K: Phosphatidylinositol 3-Kinase; pDC-TREM: Plasmacytoid Dendritic Cell-Triggering Receptor Expressed On Myeloid Cells; PIG: Plaque-Induced Genes; Plcy: Phospholipase C; PLOSL: Polycystic Lipomembranous Osteodysplasia with Sclerosing Leukoencephalopathy; PrP: Prion Protein; SHP-1: SH2-Domain-Containing Protein Tyrosine Phosphatase 1; SIGLEC-14: Sialic Acid Binding Ig-Like Lectin 14; SIGLEC-15: Sialic Acid Binding Ig-Like Lectin 15; SIGLEC-16: Sialic Acid Binding Ig-Like Lectin 16; SIGLEC-H: Sialic Acid Binding Ig-Like Lectin H; SIRP β 1: Signal Regulatory Protein-B1; sTREM2: Soluble TREM2; SYK: Spleen Tyrosine Kinase; TAM: Tyro3, AXL, and MER; TREM1: Triggering Receptor Expressed On Myeloid Cells 1; TREM2: Triggering Receptor Expressed On Myeloid Cells 2; TREM3: Triggering Receptor Expressed On Myeloid Cells 3; TREM5: Triggering Receptor Expressed On Myeloid Cells 5; TYROBP: Tyrosine Kinase Binding Protein.

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JVHM and MA wrote the manuscript. MEE and SG supervised and revised the manuscript. All authors approved the final version of the manuscript.

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