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Review

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Is TREM2 a Stretch? Implications of TREM2 Along Spinal Cord Circuits in Health, Aging, Injury, and Disease

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Abstract

Triggering Receptor on Myeloid Cells 2 (TREM2) is a receptor found in microglia within the central nervous system (CNS) but also in several other cell types throughout the body. TREM2 has been highlighted as a "double-edged sword" due to its contribution to anti- or pro-inflammatory signaling responses in a spatial, temporal, and disease-specific fashion. Many of the functions of TREM2 in relation to neurological disease have been elucidated in a variety of CNS pathologies that include neurodegenerative, traumatic and vascular injuries and autoimmune diseases. Less is known about the function of TREM2 on motoneurons and sensory neurons whose cell bodies and axons expand between the CNS and peripheral nervous system (PNS) and are exposed to a variety of TREM2 expressing cells and mechanisms. In this review, we provide a brief overview of TREM2 and then highlight literature detailing the involvement of TREM2 along the spinal cord, peripheral nerves and muscles, sensory, motor and autonomic functions in health, aging, disease, and injury. We further discuss the current feasibility of TREM2 as a potential therapeutic target to ameliorate damage in the sensorimotor circuits of spinal cord.

Keywords: neuroinflammation; Triggering Receptor Expressed on Myeloid Cells 2 (TREM2); spinal reflexes; microglia; macrophage; Motor Neuron Disease (MND); Peripheral Nerve Injury (PNI); Spinal Cord Injury (SCI); peripheral neuropathy

1. Introduction

The spinal cord facilitates communication between the central nervous system (CNS) and the rest of the body. The spinal cord contains the central projections of sensory afferents carrying information from the body, and the cell bodies and dendrites of somatic and visceral autonomic motoneurons that respectively regulate motor function in somatic and visceral muscles, by sending axons into the periphery. These neural elements interact with a variety of spinal interneurons that form local circuits that control the transfer of sensory information through the spinal cord to other CNS centers and interpret brain descending commands to exert movement of the skeletomotor system or control visceral organs (e.g., eyes, heart, gastrointestinal motility, bladder function, etc.). Within the spinal cord, some circuits organize reflexes that are rapid, involuntary motor responses to sensory inputs that can occur independently of the brain, although they are also heavily modulated by descending brain projections. Proper function of spinal reflex arcs triggered by nociceptive, mechanoreceptive, proprioceptive, and visceral receptors is key for homeostatic bodily function, movement coordination, and is also protective from damaging stimuli.

Motor Neuron Diseases (MND), Amyotrophic Lateral Sclerosis (ALS), Spinal Muscular Atrophy (SMA), peripheral neuropathies, and injuries such as spinal cord injuries and peripheral nerve injuries can have significant detrimental effects on motor, sensory, and proprioceptive functions and all include some degree of neuroinflammation. For example, in ALS, selective but progressive MN

degeneration occurs, presenting with activated glia and infiltration of inflammatory T-cells into the CNS, as well as activated monocytes and macrophages in the periphery [1–3]. Spinal cord injury causes direct damage to neural circuitry at the lesion zone but can also induce plasticity at lesion remote zones [4]. Immediately following a spinal cord injury, a patient may experience "spinal shock," during which stretch reflex circuits are suppressed or absent. Following spinal shock, surviving circuitry may result in hyperactivity and ultimately, spasticity [5]. Activation of glia and infiltration of peripheral immune cells occur at the lesion zone, but systemic immune dysfunction has also been observed, leading to secondary injuries [6–8]. Peripheral nerve injuries cause direct damage to motor and sensory neurons, leading to axon degeneration, cell death, spinal cord plasticity, permanent loss of the stretch reflex, and neuroinflammation at the site of the injury in the periphery as well as in the spinal cord where the nerves originate [9]. The consequences of neuroinflammation vary from beneficial to detrimental, depending on the disease/injury, the intensity of inflammation, and how long inflammation persists. Generally, the neuroimmune field has pushed for cell-type-specific therapies as an attempt to reduce the amount of pro-inflammatory cells or increase the amount of anti-inflammatory cells in a temporally and spatially specific manner with the ultimate goal of slowing disease progression and/or improving functional recovery following an injury or insult.

One potential target for cell-type-specific modification is Triggering Receptor Expressed in Myeloid Cells 2 (TREM2). TREM2 is found in both CNS and peripheral immune cells. It is regarded as a "double-edged sword," as knock-out rodent models have yielded beneficial or detrimental results depending on the disease model [10]. In this review, we provide a brief introduction to TREM2, followed by an examination of its potential implications in health, disease, and injury states, utilizing the spinal cord and peripheral nervous system (PNS) anatomy as a roadmap for discussing TREM2 involvement in sensory and motor neuropathologies involving the spinal cord specifically (summarized in **Figure 1**).
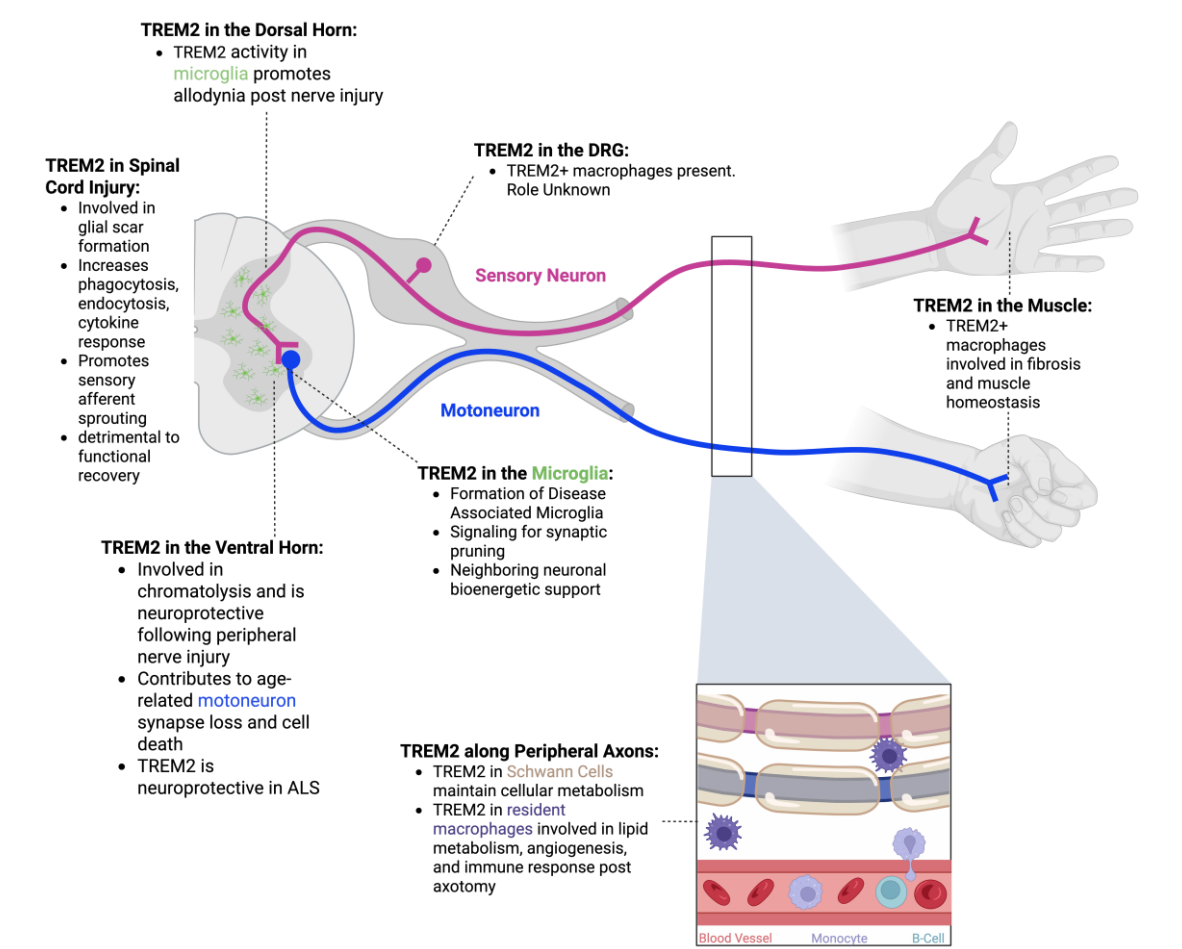
Figure 1. Graphical abstract summarizing the implications of TREM2 along spinal reflex circuitry.

2. Triggering Receptor Expressed on Myeloid Cells 2 (TREM2)

2.1. What and Where is TREM2?

TREM2 belongs to a family of transmembrane glycoprotein cell-surface receptors expressed by immune cells, including microglia. The TREM family has been extensively reviewed previously [11,12]. Here we provide a brief introduction to TREM2 specifically. The functional TREM2 protein comprises an extracellular N'-terminal receptor (IgV) domain, tethered to the transmembrane domain via a stalk, and a C'-terminal cytoplasmic domain [11,13]. TREM2 lacks a signaling motif and requires an adapter protein, such as DNAX-activating protein of 12kDa or 10kDa (DAP$_{12}$ or DAP$_{10}$), encoded by *Tyrobp* or *Hcst*, respectively, to initiate a signaling cascade [14]. The *TREM2* gene is located on chromosome 6 (6p21.1) in humans and chromosome 17C in mice and is evolutionarily conserved [11,12,15–18]. In humans, *TREM2* has five exons with six alternative splice transcripts [19,20]. The full-length human TREM2 variant which functions as a transmembrane receptor, results in 230 amino acids (227aa in mouse), whereby amino acids (aa) 1-18 is the signaling peptide, 19- 134aa is the extracellular receptor domain, 175- 195aa is the transmembrane domain, and 196- 230aa is the intracellular domain [13,21–23]. TREM2 is expressed by microglia in the CNS; Schwann cells and resident macrophages in the PNS [24]; Kupffer cells, hepatic stellate cells, and sinusoidal endothelial cells in the liver; splenic macrophages in the spleen; alveolar macrophages in the lungs; osteoclasts in bone; dendritic cells and monocyte-derived macrophages (e.g., Lipid Associated Macrophages in adipose, and resident muscle macrophages) throughout the body (extensively reviewed previously [11,20,25–27]) (**Figure 2**).
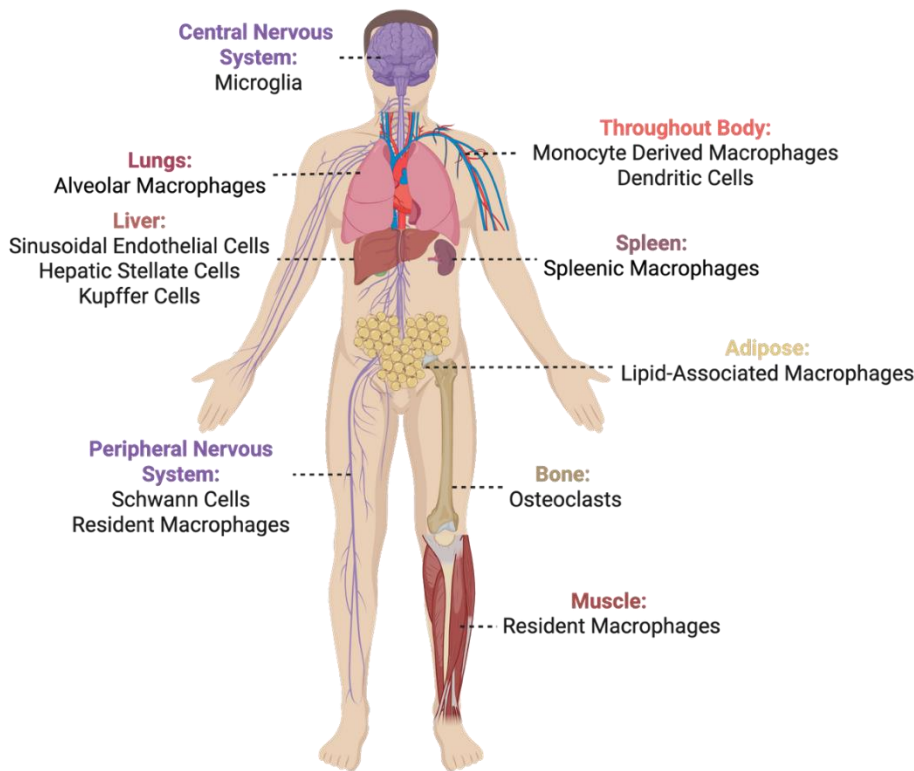
Figure 2. Cells that express TREM2 throughout the body.

2.2. TREM2 Ligands and Signaling Cascade

Numerous reviews have summarized TREM2 signaling cascades, predominantly in microglia but also in osteoclasts, Schwann cells, and peripheral macrophages. Generally, the TREM2 signaling cascade is conserved between cell types, although slight nuances may exist, primarily due to differing ligands that cell types may be exposed to. Below, we provide a comprehensive, up-to-date depiction

of the TREM2 signaling cascade surmised from the following reviews and research articles [9,11,13,20,21,23,24,27–40] (**Figure 3**).

Several ligands– including but not limited to phospholipids (e.g., phosphatidylserine)[41–44], sulfatides, lipoproteins (e.g., Apolipoprotein E, APOE) [45–47], nucleic acids [48], Lipopolysaccharide (LPS) [49], mycobacteria [50], amyloid-β [41,51], and TAR DNA-binding protein 43 (TDP-43) [52,53] bind TREM2 with high or low affinity. High avidity ligands that bind TREM2 with full affinity result in the immunoreceptor tyrosine-based activation motif (ITAM) portion of DAP12 being phosphorylated by Src family kinases [14,54]. Phosphorylated DAP12 can then allow docking and activation of Spleen Tyrosine Kinase (SYK), which robustly propagates multiple signaling cascades, including those for phosphatidylinositol 3-kinase (PI3K), Proline-rich Tyrosine Kinase 2 (PYK2), Phospholipase γ (PLCγ), Vav Guanine Nucleotide Exchange Factor 2 and 3 (VAV2/3), Mitogen-Activated Protein Kinase (MAPK) and Nuclear Factor- Kappa B (NF- ϰB), ultimately leading to increased cell survival, cytoskeletal rearrangement, proliferation, phagocytosis, and release of inflammatory chemokines [9,11,20,21,23,24,28–40] (**Figure 3**). Low-avidity ligands that bind TREM2 with partial affinity result in activation of SH2-containing inositol 5'-phosphatase-1 (SHIP1), which inhibits SYK and downstream signaling cascades [11,14,39]. TREM2 signaling can also be modulated by other receptors, such as Colony Stimulating Factor 1 Receptor (CSF1-R), that bind ligands CSF1 and Interleukin-34 (IL-34). Upon activation, CSF1-R phosphorylates SRC [55] to activate PI3K/ERK signaling cascades, leading to cell proliferation and increased transcription of several downstream signaling molecules, including *Tyrobp* (DAP12) [9,56–60]. In addition to transcriptional changes, CSF1-R and TREM2 are frequently found close to each other and can interact either through DAP12-SRC signaling or physically by their transmembrane domains [38,43,59] (**Figure 3**). DAP12 and SYK are utilized in numerous other signaling cascades not discussed here that increase the complexity of immune cell signaling. Collectively, the literature suggests that TREM2 is just one modulatory receptor in a complex web that varies depending on cell type and microenvironment.
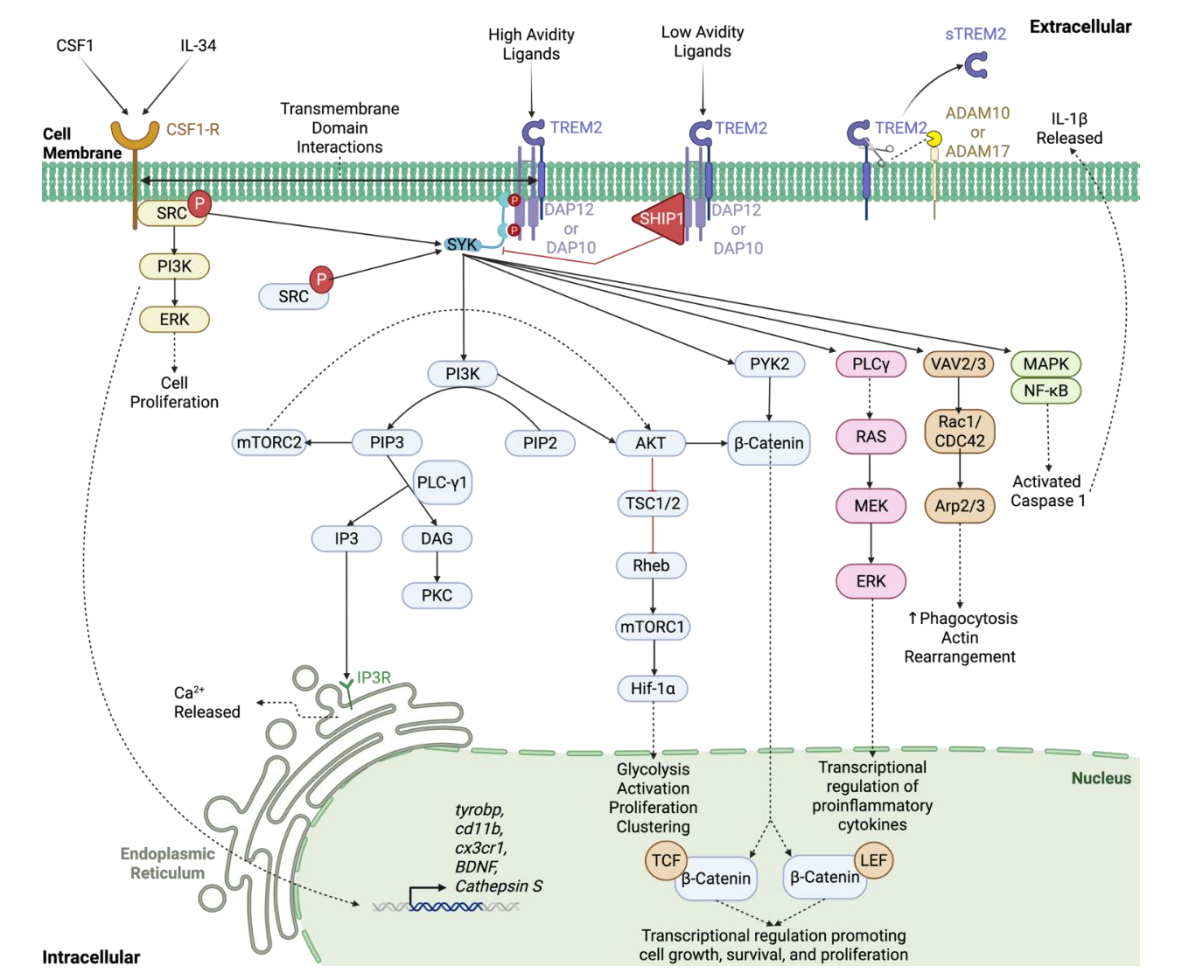
Figure 3. TREM2 Signaling Cascade.

Colony Stimulating Factor 1 (CSF1), Interleukin-34 (IL-34), Colony Stimulating Factor 1 Receptor (CSF1-R), Src Family Kinases (SRC), phosphatidylinositol 3-kinase (PI3K), Extracellular signal Regulated Kinase (ERK), Triggering Receptor Expressed on Myeloid Cells 2 (TREM2), DNAX activation protein of 12kDa (DAP12), DNAX activation protein of 10kDa (DAP10), SYK (Spleen Tyrosine Kinase), phosphatidylinositol-4,5-bisphosphate (PIP2), phosphatidylinositol-3,4,5-trisphosphate (PIP3), mammalian target Of Rapamycin Complex 2 (mTORC2), Phospholipase γ1 (PLC-γ1), diacylglycerol (DAG), inositol trisphosphate (IP3), Protein Kinase C (PKC), inositol trisphosphate receptor (IP3R), Calcium (Ca^{2+}), Protein Kinase B (AKT), Tuberous Sclerosis Complex-1 and -2 (TSC1/2), Ras homolog enriched in brain (Rheb), mammalian target Of Rapamycin Complex 1 (mTORC1), Hypoxia-inducible factor 1-alpha (Hif-1α), Proline-rich Tyrosine Kinase 2 (PYK2), T-cell factor (TCF), Lymphoid Enhancer-binding Factor (LEF), Phospholipase γ (PLC-γ), Mitogen-activated protein kinase kinase (MEK), Vav Guanine Nucleotide Exchange Factor 2 and 3 (VAV2/3), Ras-related C3 botulinum toxin substrate 1 (Rac1), Cell division control protein 42 homolog (CDC42), actin-related protein 2/3 (Arp2/3), Mitogen-Activated Protein Kinase (MAPK), Nuclear Factor-$\varkappa$B (NF-$\varkappa$B), Interleukin-1β (IL-1β), soluble TREM2 (sTREM2), A Disintegrin and Metalloprotease 10 (ADAM10), A Disintegrin and Metalloprotease 17 (ADAM17), SH2-containing inositol 5′-phosphatase-1 (SHIP1).

2.3. sTREM2

Soluble TREM2 (sTREM2) is a truncated TREM2 variant comprising the receptor domain and a fragment of the stalk [13]. The sTREM2 protein variant can result either from cleavage of the full-length TREM2 or secretion of alternative splice variants [13,22,61]. A Distintegrin and Metalloprotease 10 and/or 17 (ADAM10 and/or ADAM17) have been shown to cleave full-length TREM2 at the H157-S158 bond in the stalk, which allows shedding of the ectodomain, sTREM, into the microenvironment [11,13,22,23,61–64] (**Figure 3**). The remaining transmembrane domain can be further cleaved by γ-secretase, releasing the intracellular domain for proteolysis [22,63]. Two alternative splice isoforms of TREM2, which lack the transmembrane domain, can also be translated into sTREM2, which is subsequently released extracellularly [19,65–67]. Once released by either mechanism, sTREM2 can be detected in the extracellular space, cerebrospinal fluid, and serum [11,13,68,69]. sTREM2 has been extensively studied in Alzheimer's disease (AD), but has also been found in other motor/spinal neuropathologies such as ALS, and following spinal cord injury [69]. Although the exact mechanisms and function of sTREM2 remain to be fully elucidated, it has been found to function independently from TREM2 by 1) interacting with neighboring cells in a non-cell autonomous manner, 2) autocrine signaling, and 3) scavenging excess TREM2 ligands [11,13,48,62,65,70–72]. In AD, sTREM2 is theorized to perpetuate neuroinflammation, promote immune cell survival, and increase phagocytosis of protein aggregates, debris, and damaged neurons, as the level of sTREM2 in cerebrospinal fluid and serum correlates with disease progression [39,73–75]. Alternatively, sTREM2 may be useful as a biomarker for neurodegeneration following injury or disease. Individuals with ALS have been shown to have elevated TREM2 protein in the spinal cord, and significantly greater sTREM2 in cerebrospinal fluid and serum compared to healthy controls [69,76]. Further, the level of cerebrospinal fluid sTREM2 has been shown to predict patient survival duration [77]. In spinal cord injury, elevated cerebrospinal fluid sTREM2 has also been identified and correlates with neurodegeneration markers (e.g., neurofilament light chain) within the first two months post-injury, suggesting sTREM2 may be a biomarker for injury severity [78].

2.4. TREM2/DAP12 Mutations in Disease

Some *TREM2* mutations have been identified that alter function and can be either disease-causing or risk factors for certain diseases. Polycystic Lipomembranous Osteodysplasia with Sclerosing Leukoencephalopathy (PLOSL), also known as Nasu-Hakola disease, is caused by

recessive inheritance of homozygous loss-of-function mutations of TREM2 or DAP12 [79–81]. This disease is characterized by cysts developing on the bones as well as a characteristic presenile dementia, similar in progression to Frontotemporal Dementia (FTD) [81]. However, loss-of-function TREM2 mutations can also cause FTD-like dementias without the presence of bone cysts [82]. While the link of Nasu-Hakola disease to TREM2/DAP12 signaling is well established, the exact disease mechanisms have yet to be elucidated due to the inability of mouse models to recapitulate the disease.

The role of TREM2 variants in other disease models is less clear and frequently highly debated. The R47H TREM2 mutation substitutes an arginine for a histidine near the ligand-binding site and was discovered to be a risk factor for developing AD [82,83]. This discovery was the first to directly connect TREM2 dysfunction to AD development later in life. TREM2's role in AD has been studied and described in depth by many groups [82–87]. Briefly, the connection between TREM2 function and AD is supported by showing that *Trem2* gene deletions increase Tau interneuronal dispersion [84], decrease amyloid-β plaque clearing [88], and worsen disease prognosis in mouse models. Similarly, the R47H variant has reduced affinity for amyloid-β, and this variant may hasten AD progression due to an increased affinity for externalized phosphatidylserine (ePtdSer), an "eat me" signal that can prompt synapse removal and worsen neurodegeneration [85].

Further studies extended the role of the R47H mutation to other neurodegenerative disorders, including PD [89]. However, when this mutation was investigated in the spinal cord as a potential risk factor for ALS, the results varied. Some studies proposed the R47H mutation as a risk factor in sporadic ALS [90]. However, other groups found no significant relationship in human patient populations between this genetic mutation and sporadic ALS [86]. Other *TREM2* mutations have been studied regarding ALS as well as FTD; their potential as risk factors is also debated [86,91]. Nevertheless, some homozygous and compound heterozygous mutations in exon 2 can be causative for FTD [91].

2.5. Different Mouse Models May Contribute to Conflicting TREM2 Results

One problem is that TREM2's functional complexity throughout development and after disease onset may induce confounding effects. The most used Global TREM2 Knockout (GKO) mouse model has a 175bp deletion and introduces an early stop codon after bp17, leaving no functional protein isoform (Jax #027197) [92]. The benefit of this model is a complete absence of TREM2 signaling. However, TREM2's actions during normal developmental synaptic pruning introduce confounds when studies look at aberrant circuitry caused by injury or disease [93]. Moreover, these results could be region-specific [94–96], and the unknown action in other brain cells and the peripheral immune system can introduce pleiotropic effects that are difficult to control. Further, TREM2 GKO can lead to conflicting conclusions depending on the neurodegenerative mouse model. For example, Lyens et al. (2017) found that in a pure tauopathy model of AD, *Trem2* knockout was beneficial and neuroprotective [97]. Two years later, the same group in Lyens et al. (2019) found *Trem2* knockout and the R47H variant to be detrimental in an APPPS1-21 mouse model of AD [98]. This highlights the importance of the nuances of TREM2 signaling in various mouse models of disease.

In contrast, conditional TREM2 Knockout (cKO) models have the benefit of being cell-type specific and potentially temporally controlled. This model usually involves a floxed mouse model that removes exons 2 and 3 from *Trem2* after recombination (Jax #029853) [99]. However, there are some studies suggesting that a *Trem2* variant can still be generated without these exons [100]. The extent of signaling that can occur without the presence of exon 2, where the ligand binding domain is located, has yet to be fully characterized; however, this TREM2 isoform variant could still fold and localize normally even without exons 2 and 3 [100].

3. The Dorsal Root Ganglion

3.1. Anatomical Overview of the Dorsal Root Ganglion

The Dorsal Root Ganglion (DRG) is a complex structure situated bilaterally within the dural sheath, within the vertebral foramina, outside of the spinal cord [101]. As an enlargement of the dorsal root, a single DRG houses the cell bodies of pseudo-unipolar sensory neurons, ranging from 15,000 neurons in rats to 70,000 in humans, with variability depending on the spinal segment [102–105]. The bifurcating axons of DRG neurons extend peripherally to innervate sensory receptors or end freely in skin, muscle, and viscera, whereas the central branches enter the spinal cord, allowing information from the periphery to reach the CNS. Given the peculiar anatomy, DRG sensory neurons and their axons interact with many different cell types and tissues, which include myelinating or non-myelinating Schwann cells in peripheral nerves and oligodendrocytes centrally, whereas the cell body is surrounded by satellite glial cells. In addition, fibroblasts, pericytes, mast cells, endothelial cells, resident macrophages, and monocyte-derived macrophages can also be found among the connective tissue within the DRG and in peripheral nerves, while microglia interact with the central branches of sensory axons [106]. Following injury or in diseases such as diabetic neuropathy, communication from the periphery to the CNS is compromised [107,108]. Therefore, identifying mechanisms that can preserve, prevent, or prolong detriments is crucial for improving patient prognosis in injury and disease. In the following section, we will discuss the current knowledge of TREM2 in the DRG.

3.2. TREM2 in the Dorsal Root Ganglion

Although numerous RNA sequencing studies have found macrophages with high levels of *Trem2* and *Tyrobp* expression in the DRG following injury or in diseased states, the exact role of these TREM2/DAP$_{12}$+ cells is currently unknown [107,109–111]. Some literature suggests that macrophages in the DRG are specifically involved in the initiation and maintenance of mechanical hypersensitivity following peripheral nerve injury, as DRG macrophage depletion prevents and/or stops neuropathic pain [112]. In 2023, Feng et al. identified four different populations of macrophages in the DRG following peripheral nerve injury: 1) bone-marrow-derived precursor cells, 2) self-renewing macrophages, 3) microglia-like macrophages, and 4) satellite glial cell-like macrophages [113]. The potential differential expression and signaling of TREM2 in different DRG macrophage subpopulations remains to be elucidated. Research on the role of TREM2 in other diseases and injuries suggests that TREM2+ DRG macrophages may regulate the local cytokine response (either pro- or anti-inflammatory) and influence the metabolic processes of neighboring cells; however, TREM2 in the DRG is currently understudied (**Figure 1**).

4. TREM2 in the Spinal Cord

4.1. Anatomical Overview of the Spinal Cord

The spinal cord is a complex CNS region that contains circuits that can act independently from the brain or transmit sensory, motor, or autonomic signals between the brain and peripheral targets. The spinal cord can be divided into five regions, each with different segments that innervate different regions of the body via bilateral peripheral spinal nerve pairs. Humans have 31 segments: cervical (C1-C8), thoracic (T1-T12), lumbar (L1-L5), sacral (S1-S5), and one coccygeal; these vary slightly in different species (mouse: 8 cervical, 13 thoracic, 6 lumbar, 4 sacral, and 3 coccygeal). Spinal cord segments contain specific circuitry that controls different body regions and functions. For example, all segments are capable of transmitting sensory information from cutaneous organs informing about touch (mechanoreceptors) or pain (nociception) or from muscles and joints (proprioception). All segments contain somatic motor neurons whose outputs control muscle contractions in the corresponding segments. Similarly, all segments have circuitry to evoke nociceptive flexion reflexes (i.e., withdrawal reflex) and proprioceptive reflexes (i.e., stretch reflex). Other circuits and functions are more specific to certain segments. The cervical and upper thoracic spinal cord contains circuitry

for tectospinal reflexes coordinating eye and neck muscles, as well as respiratory reflexes that control diaphragm and intercostal muscles. Thoracic and upper lumbar regions contain circuitry that controls the autonomic sympathetic system and encodes visceral reflexes for cardiovascular control. The sacral and coccygeal regions predominantly contain reflexive circuitry for the pelvic area, including urination, defecation, and reproductive organs controlled by specialized somatic motor neurons and autonomic parasympathetic neurons [114–119]. Disease or injury may affect differentially specific spinal cord segments, causing a plethora of different combinations of sensory, motor, or visceral dysfunction and symptoms.

Although functional and cellular differences exist between spinal segments, all have the same general anatomy. The central projection of sensory neuron afferents enters the dorsal horn of the spinal cord through the dorsal root. Nociceptive sensory neurons terminate on interneurons in lamina I-II; mechanoreceptive sensory neurons terminate on interneurons in lamina III-V; and proprioceptive sensory neurons terminate either on interneurons in lamina V or on motoneurons in lamina IX. Motoneuron cell bodies are located in the ventral horn, and their axons exit through the ventral root [114] (**Figure 4**). Sensorimotor integration function in the spinal cord occurs through reflex circuits that commonly experience plasticity during development, aging, disease, and after injury. The removal of synapses or damaged neurons during aging, disease, and injury is frequently attributed to microglia. Microglia are the primary spinal cord cells that contain TREM2; however, in diseased or injured states, TREM2+ peripheral macrophages may enter the spinal cord as well. In this section, we will discuss the role of TREM2 in microglia function broadly, followed by the implications of TREM2 in the dorsal and ventral horns, and following spinal cord injury.
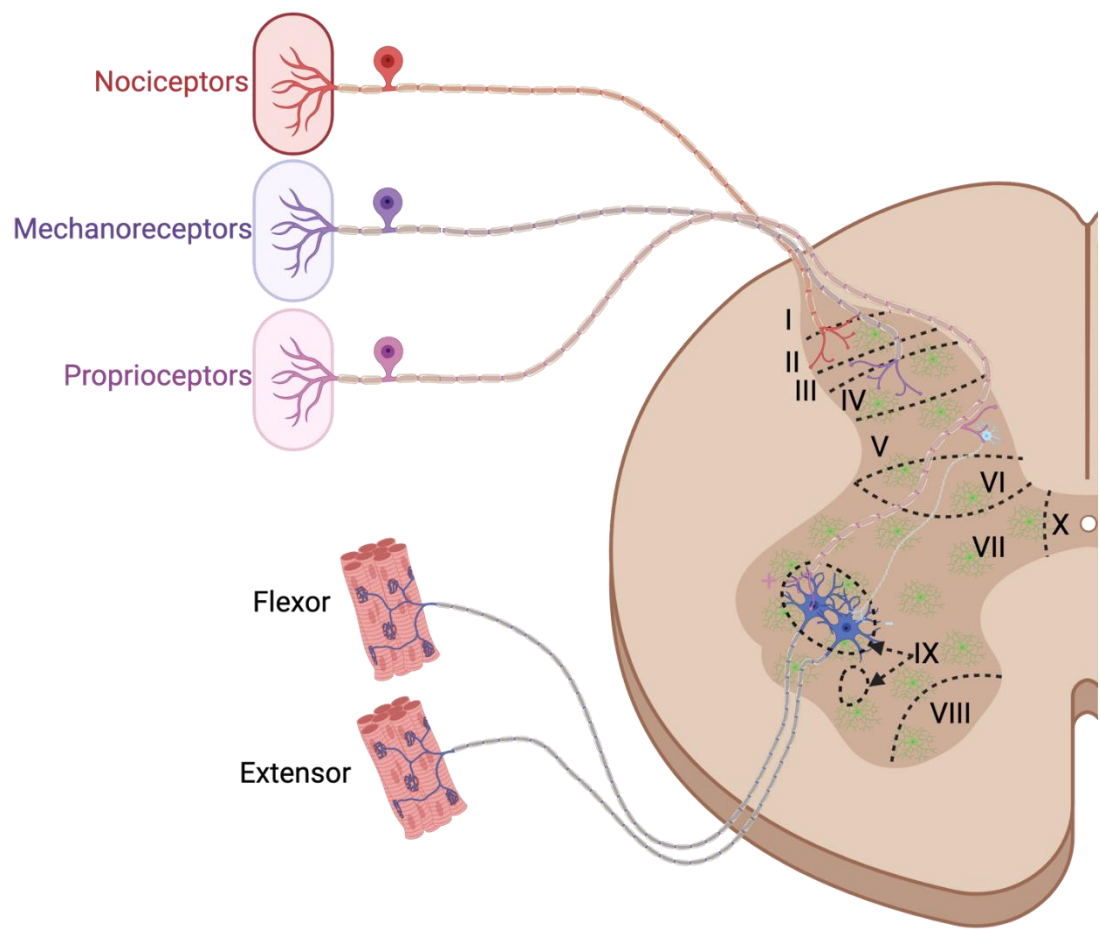
Figure 4. Simplified illustration of spinal reflex circuitry. Figure illustrates the different types of sensory neurons and where they terminate within a lumbar spinal cord segment. Nociceptors (red) terminate on interneurons (not shown) in lamina I-II, mechanoreceptors (purple) terminate on interneurons (not shown) in lamina III-IV, and proprioceptors (pink) terminate on interneurons in lamina V (light blue) and motoneurons in lamina IX

(dark blue). Microglia (green), the spinal cord's resident immune cell, are predominantly responsible for synapse and neuron removal in healthy development, aging, disease, and injury and express TREM2.

5. TREM2 in Microglia

5.1. Disease-Associated Microglia

High TREM2 expression is frequently associated with a subtype of activated microglia known as Disease-Associated Microglia (DAM). Morphologically, DAM typically have enlarged cell bodies and reduced processes, resulting in an ameboid appearance compared to ramified surveying microglia in healthy tissue [120–123]. DAM were first characterized in AD mouse models and human post-mortem tissue as they are found around amyloid-β plaques and in proximity to apoptotic neurons; however, DAM have also been found in ALS, PD, peripheral nerve injury, spinal cord injury, and aging rodent models [123–127]. Through RNA sequencing and immunohistochemistry in various neuropathologies, DAM have been characterized by elevated expression of Trem2, Tyrobp, Apoe, Lpl (Lipoprotein Lipase), and Ctsd (Cathepsin D), cumulatively deeming their typical function as pro-inflammatory, lipid metabolizing, and highly phagocytic activated microglia cells [125–131]. The formation of DAM from surveying microglia has been generally accepted to be a two-stage process, whereby Stage 1 is TREM2-independent, and Stage 2 is TREM2-dependent. Stage 1 involves the downregulation of homeostatic genes (e.g., Cx3cr1 and Tmem119) as well as the upregulation of Trem2, Tyrobp, and Apoe. TREM2-dependent Stage 2 results in expression changes of genes involved in phagocytosis and lipid metabolism (e.g., Lpl and Ctsd) [125,126,128,129]. Research suggests the increase in APOE expression helps sustain TREM2 activation in an autocrine/paracrine loop fashion [132]. Further, as discussed above, TREM2 activity results in pro-proliferative and pro-survival signaling cascades, which maintain microgliosis in diseased or injured states [129]. Genetic TREM2 knockout or xenotransplanted human knockout microglia in AD mouse models (5XFAD), and TREM2 knockout in ALS mouse models (SOD1) all result in fewer DAM [87,127,133]. Further, knockout of SYK, a downstream target of activated TREM2, also results in reduced phagocytosis and DAM formation [134]. In contrast, we recently reported that microglial TREM2 knockout mice still develop what appear to be DAM following peripheral nerve injury, although their microglial function is compromised [123]. Collectively, this highlights 1) the necessity to investigate microglial TREM2 in additional disease and injury models, 2) TREM2 function is variable depending on each cell's microenvironment, and 3) DAM formation may occur through compensatory pathways activated in certain disease or injury states.

5.2. Synaptic Plasticity

TREM2 has also been shown to be involved in synaptic plasticity; however, its exact role in synapse removal is complex [135]. Filipello et al. (2018) demonstrated that TREM2 is required for the canonical synaptic pruning during developmental circuit and behavior refinement. Juvenile TREM2 knockout mice result in increased cortical synaptic density, excess excitatory neurotransmission, reduced functional brain connectivity, and ultimately, social behavior deficits [93]. However, the lack of synaptic pruning may contribute to reduced synaptic stabilization, as adult TREM2 knockout mice had reduced, instead of larger, synaptic density [93]. In agreement, Jay *et al*. (2019) found that TREM2 knockout resulted in decreased synaptic density in one-month-old mice; however, they mechanistically proposed that microglia TREM2 limits astrocytic synapse engulfment during development [136]. Intriguingly, post-mortem cortex from five to 23-year-old idiopathic autistic humans had reduced TREM2 compared to control tissue, and TREM2 levels inversely correlated with the individuals' Autism Diagnosis Interview-Revised (ADI-R) score, suggesting microglial TREM2 is necessary for normal canonical neuronal circuit development [93]. Recently, Vecchiarelli et al. (2024) published evidence that a particular TREM2-dependent microglia phenotype that is frequently missed by immunohistochemistry, "Dark Microglia," arises at crucial developmental periods, whereby the Dark microglia perform endocytosis and trogocytosis for synaptic and vascular

remodeling [137,138]. Additional studies reveal further complexities of TREM2 involvement with synaptic plasticity.

During development, microglia often utilize C1q and the complement cascade to prune synapses selectively [139–141]. The signal to initiate complement-mediated synapse pruning was proposed to be initiated by TREM2 recognition of externalized phosphatidylserine (ePtdSer) at synaptic sites [142]. PtdSer is normally located on the inner leaflet of the lipid bilayer, but in disease and injury states, PtdSer can be externalized. ePtdSer is a known "eat me" signal and high-affinity ligand of TREM2 [42]. Nevertheless, a built-in TREM2 feedback mechanism also seems to be at play, negatively modulating synapse pruning. In AD rodent models, amyloid-β and tau also result in increased C1q, complement pathway activation, and synapse elimination [143–145]. Zhong et al. (2023) found microglial TREM2 binds C1q with high affinity in 5xFAD mice and postmortem human AD cortex to minimize complement-mediated synaptic loss. Thus, TREM2 knockout resulted in accelerated synapse elimination, suggesting that TREM2 prevents synapse loss in AD [146]. However, Rueda-Carrasco et al. (2023) provided evidence that in the early stage of an AD mouse (hAPP NF-L knock-in mouse), hyperactive synapses display ePtdSer and are preferentially removed by microglia via TREM2. The authors conclude that TREM2 is beneficial, by selectively removing inefficient synapses, not because of synapse preservation [147]. A similar conclusion was reached by Fracassi et al. (2023) in that non-demented individuals with AD neuropathology are protected by higher-than-normal TREM2 activity detecting ePtdSer in dysfunctional synapses, triggering their removal by microglia [148]. The discrepancy between these various studies may be explained by the use of different mouse models and analyses at different disease stages, but all highlight that TREM2 has complex activities in synaptic plasticity by interfering with multiple mechanisms of synapse deletion/preservation. Dejanovic et al. (2022) highlight differential effects of TREM2 on microglia versus astrocytic engulfment of inhibitory versus excitatory synapses in various models of AD, creating synaptic imbalances affecting network function [149]. Moreover, TREM2 actions on synapses might be regionally dependent. TREM2-R47H variant results in increases of synapses in the cortex but not in the hippocampal regions [150]. Thus, synapse deletion might occur through a multiplicity of mechanisms in different disease states, synapses, and regions, with TREM2 affecting their balance and having differential effects, sometimes beneficial and others detrimental. The role of TREM2 in spinal cord synaptic plasticity in disease or following an injury has been much less studied. Brennan et al. (2024) recently reported specific deletion of inhibitory synapses controlling sympathetic outflow by a TREM2 microglia mechanism after spinal cord injury, contributing to autonomic dysreflexia [151].

5.3. Neuronal Bioenergetic Support

Microglia have been shown to routinely monitor and therefore rapidly respond to neuronal mitochondrial states in health and following injury via specialized microglial P2RY12-neuronal KV2.1 junctions [152]. However, literature also suggests alternative microglial receptors may influence microglia's aid in neuronal bioenergetic support. In 2019, Tagliatti et al. provided novel evidence that microglial TREM2 is necessary for hippocampal CA1 pyramidal neuron bioenergetics. In this study, TREM2 knockout postnatal day 1 (p1) mice resulted in reduced hippocampal basal mitochondrial metabolism. Excitatory pyramidal and granular cells specifically resulted in altered gene expression for mTOR and mitochondrial pathways (including mitochondrial machinery and oxidative phosphorylation components) and delayed maturation compared to wild-type TREM2 littermates. Further, as expected, TREM2 knockout resulted in altered synaptic pruning. Intriguingly, the effect of TREM2 knockout was not universal, as neither CA3 excitatory neurons nor inhibitory neurons were significantly affected. CA1 was also found to have significantly higher amounts of TREM2 than CA3 in wildtype mice. This work suggests that some neuronal subpopulations or neurons in certain states may be more dependent on microglial TREM2 than others, and that microglial TREM2 is necessary for normal developing neurons' mitochondrial metabolism [94]. Currently, it is largely unknown how microglial TREM2 affects neuronal bioenergetics in spinal

neurons or motoneurons during disease or after injury, where there is a high metabolic demand for survival. Our studies have suggested that in the absence of microglia TREM2 there is a dysregulation in motoneurons of the normal cell body reaction to axotomy and in preparation to switching towards a regenerative metabolism (see below).

6. TREM2 In the Dorsal Horn

6.1. Neuropathic Pain

Physiological pain is crucial for detecting and responding to noxious stimuli. As discussed above, the flexion withdrawal reflex depends on cutaneous nociceptors to detect painful stimuli and rapidly withdraw that part of the body from a potentially damaging stimulus. However, if pain persists post-healing or during disease, it becomes pathological. Identifying mechanisms to remedy pain sensation without compromising healing is essential for therapeutic advancement. In this section, we will discuss TREM2's involvement in microglia function in various neuropathic pain conditions.

Following a peripheral nerve injury, neuropathic pain frequently persists in addition to permanent motor and proprioceptive deficits[123]. It is generally accepted that dorsal horn microglia contribute to plasticity, which facilitates prolonged hypersensitivity following peripheral nerve injury [153–166]. We have previously reviewed the mechanisms of microglia activation and general hypotheses behind microgliosis around the central branches of sensory afferents injured in the peripheral nerve, and therefore, will not be discussing them in detail here [9]. Given that microglia contribute to neuropathic pain, identifying mechanisms that alter microgliosis may provide options as therapeutic targets. Microglial TREM2 has increasingly been investigated as a mechanism of microglia-induced allodynia following peripheral nerve injury.

Numerous studies in rodent models have reported an increase in dorsal horn microglial TREM2 and DAP_{12} expression and phosphorylation following peripheral nerve injury [59,167–169]. In 2016, two publications provided evidence that either TREM2 or DAP_{12} deficiency can reduce allodynia following peripheral nerve injury. Guan et al. (2016) provided RNA sequencing evidence of increased dorsal horn *Tyrobp* (DAP_{12}) expression as early as one day post sciatic nerve cut-ligation. In rats, animals that performed pain-induced self-mutilation of the injured limb (autotomy) had higher DAP_{12} expression than littermates with no evidence of autotomy, suggesting allodynia may be mediated by DAP_{12} signaling. This was confirmed as DAP_{12}-deficient mice had reduced allodynia, evident by increased mechanical thresholds for pain [59]. Later that year, Kobayashi et al. (2016) confirmed these findings and showed that following an L4 nerve injury, dorsal horn microglia increase TREM2 and DAP_{12} expression and activity, evident by increased DAP_{12} phosphorylation. The increase in TREM2/DAP_{12} activity resulted in an increased production of proinflammatory cytokines and purinergic receptors (TNFα, IL-1β, IL-6, P2RX4), ultimately leading to increased pain post-injury. Again, DAP_{12}-deficient mice exhibited decreased inflammation and allodynia with improved recovery time. Perhaps the most convincing of direct TREM2 involvement in the regulation of sensory nociceptive thresholds was the intrathecal injection of a TREM2 agonist-induced allodynia via DAP_{12} activity [167]. Tansley et al. (2022) further elucidated the role of TREM2-mediated allodynia in a spared nerve injury rat model. Intrathecal injection of TREM2 lentivirus or an autophagy inhibitor (3-MA) both led to increased mechanical allodynia. Suggesting a TREM2-autophagy pathway which modulates microglia function and neuroinflammation following peripheral nerve injury [168]. The expansion of the RNA sequencing literature has supported the notion of dorsal horn microglial heterogeneity. Recently, a specific cluster of microglia, identified as *Cd11c+*, was found to appear following peripheral nerve injury and deemed necessary for spontaneous allodynia recovery, as CD11c+ microglia depletion relapsed injury-induced pain sensitivity. This subpopulation of microglia was theorized to appear upon myelin consumption from damaged primary afferents. Intriguingly, mice with TREM2 deficiency have impaired appearance of CD11c+ microglia [170,171]. In AD rodent models, CD11c was found to be another marker of DAM [125,172]. Based on this, it is suggested that the identified CD11c+ microglia, which appear following myelin consumption in the

dorsal horn, are TREM2-dependent DAM that contribute to allodynia post-peripheral nerve injury. Collectively, this cumulative evidence in the literature suggests that peripheral nerve injury increases microglial TREM2 signaling, thus contributing to neuropathic pain states and a decrease in sensory thresholds to cutaneous stimuli.

TREM2 activity's influence on microglia function may be more specific to females. In a recent study using a mouse sciatic nerve chronic constriction injury model, ipsilateral spinal microglia RNA sequencing data were submitted to QIAGEN's Ingenuity Pathway Analysis to help identify the physiological function and upstream regulators of transcriptional changes between males and females seven days post-injury. Identified male microglia upstream regulators included activation of Interferon Regulatory Factor 3 and 7 (IRF3/IRF7), whereas female microglia included activation of TREM2 and Interferon-γ. The authors suggested sexual dimorphisms in microglial transcriptional signatures, which may contribute to differences in pain-processing and thresholds post-peripheral nerve injury [173]. Recently, we showed evidence suggesting that ventral horn DAM-like microglia in females have elevated TREM2 compared to males, with sex-specific TREM2 knock-out effects, supporting the notion that female microglia may utilize TREM2 activity more than males [123].

Neuropathic pain is also frequently a co-morbidity of other pathologies, such as diabetic neuropathy. Type I diabetes mellitus can be modeled in rodents via intraperitoneal administration of Streptozotocin (STZ), and results in painful diabetic neuropathy, evident by spinal cord neuroinflammation, axon degeneration, and reduced mechanical withdrawal and thermal withdrawal thresholds. Chen et al. (2021) identified a marked increase in TREM2 and DAP$_{12}$ expression between one and two weeks post-Streptozotocin injection. Over-expression of TREM2 via intrathecal infusion of a microglia-specific lentivirus resulted in increased microglial number, CD68 (indicating increased phagocytosis), increased production of pro-inflammatory IL-1β, and reduced expression of anti-inflammatory TGF-β and IL-10. Blocking TREM2 activity via an intrathecal injection of TREM2-neutralizing antibody resulted in the opposite effects [174]. This work supports the theory that dorsal horn TREM2 activity contributes to neuroinflammation-mediated chronic pain in diabetic neuropathy models, similar to post-peripheral nerve injury and neurodegenerative diseases.

Bone fractures and orthopedic surgery resulting in neuropathic pain are resistant to current analgesics, which further warrants research to identify pharmacological targets for pain relief. An anti-malaria drug, Artesunate, was proposed as a potential pain-relief treatment due to its anti-inflammatory properties [175,176]; however, if and how Artesunate might aid in neuropathic pain from fractures and orthopedic surgery was unknown. Zhang et al. (2022) found that intrathecal injection of Artesunate four to six days following a bone fracture ameliorated neuropathic pain by inhibiting upregulation of CCL21, TREM2, and DAP$_{12,}$ resulting in reduced allodynia evident by improved mechanical and thermal thresholds [177]. Other research has shown that Artesunate treatment in the periphery following peripheral nerve injury also improves nerve regeneration and reduces inflammation, although it is unknown if the effects are also TREM2-mediated [178].

Chemotherapy is known to induce peripheral neuropathy and microglia-mediated neuropathic pain [179–183]. Chemotherapy agent, Cisplatin, was found to induce prolonged microgliosis in Lumbar 4-6 dorsal horn and increase microglial TREM2 and DAP$_{12}$ expression. Strikingly, intrathecal injection of an anti-TREM2 neutralizing antibody 30 minutes post Cisplatin administration resulted in reduced proinflammatory cytokines (IL-6, TNFα, iNOS), increased anti-inflammatory cytokines (IL-4, IL-10), reduced allodynia, and reduced the loss of small nerve fibers in the periphery. This suggests that Cisplatin-induced neuropathic pain may be mediated by TREM2/DAP$_{12}$ signaling [180].
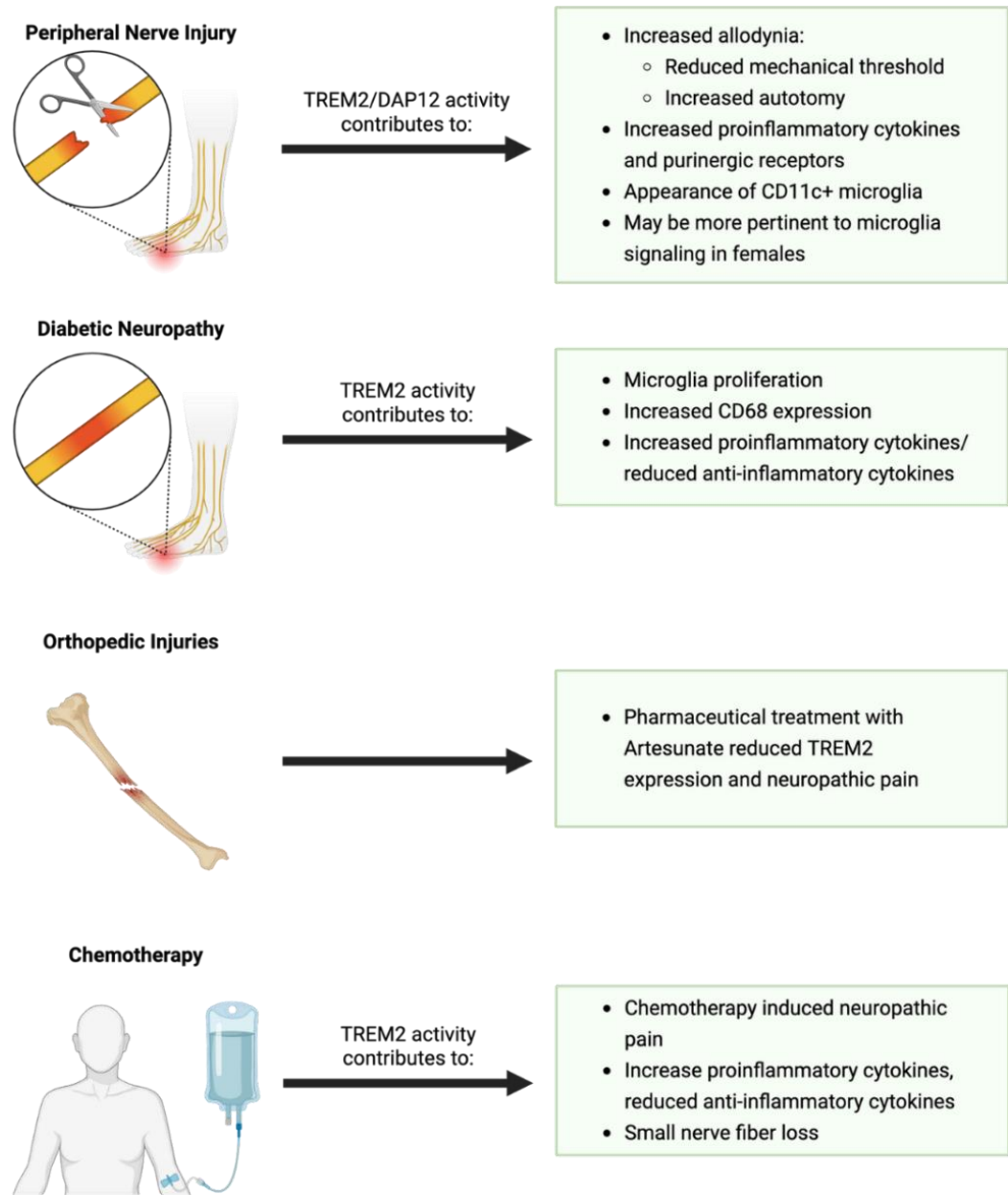
Figure 5. TREM2 contributions to dorsal horn inflammation and allodynia in four neuropathic pain conditions.

Collectively, the literature suggests dorsal horn TREM2/DAP$_{12}$ activity contributes to neuropathic pain regardless of injury type and thus suggests it as a potential therapeutic target for analgesic drug development (**Figure 1, Figure 5**).

7. TREM2 in the Ventral Horn

7.1. Peripheral Nerve Injury

Microglia are known to have complex interactions with healthy and injured motoneuron cell bodies and dendrites located in the ventral horn [9,123,184–188]. Following a peripheral nerve injury, microglia become activated, proliferate, migrate, and adhere to motoneuron cell bodies with a heterogeneity of microglia morphological phenotypes [123,187]. Following a peripheral nerve injury, microglial TREM2 and DAP$_{12}$ expression, as well as phosphorylation of downstream SYK, increase near motoneuron cell bodies [123,189,190]. Subpopulations of microglia that express the highest levels of TREM2 frequently display signs of elevated phagocytic marker, CD68, compared to alternative neighboring microglia phenotypes [123,189]. Following hypoglossal nerve injury, microglia in DAP$_{12}$-deficient mice had reduced expression of pro-inflammatory cytokines and

prevention of motoneuron cell death in the hypoglossal nucleus, suggesting a neuroprotective role for TREM2 [190]. In support of this, we recently provided evidence from global and conditional TREM2 knockout mice that microglial TREM2 is necessary for canonical chromatolysis following sciatic nerve axotomy [123]. Chromatolysis is generally regarded as a morphological sign of regenerative capacity that parallels the exponential increase in RNA and protein synthesis required for axon regeneration [191,192]. In addition, we found TREM2 highly expressed in microglia macroclusters with typical characteristics of DAM that also contained high numbers of large CD68 granules, suggesting macro-phagocytic activity. These microglia clusters are always associated with degenerating motoneurons and attract infiltrating CD8+ T-cells [187]. TREM2 deletion did not alter the formation of these clusters but decreased the intensity of phagocytic markers. Collectively, these results suggest that TREM2 activity in the ventral horn after peripheral nerve injuries has a dual function: first, it may facilitate the regenerative phenotype of some motoneurons; second, it may promote cell death and/or clearance of other motoneurons.

7.2. Aging

Aging gradually increases microglial activation, phagocytosis, and contacts with the cell bodies and excitatory synapses of α-motoneurons in the ventral horn of mice [193]. These findings suggest that microglia may play a role in either motoneuron maintenance with age or on their decline, resulting in loss of motor force and increased fatigability with age. RNA sequencing of microglia from aged mice shows an increase in pro-inflammatory and DAM markers (e.g., *Spp1*, *Lpl*, *Apoe)* and indicates TREM2 as an upstream regulator of aging-related transcriptional changes [193]. Additionally, motoneurons show increased expression of APOE, a TREM2 ligand, with age [194]. These results may point to a preferential effect on motoneuron demise and suggest the APOE-TREM2 pathway as a potential therapeutic target for mitigating aging-related motor decline (**Figure 1**).

7.3. Amyotrophic Lateral Sclerosis

Selective and progressive loss of motoneurons accompanied by neuroinflammation in the spinal cord is a hallmark of ALS. Literature suggests a duality of microglia function in ALS, as microglia generally have an anti-inflammatory neuroprotective role at early disease timepoints and gradually become pro-inflammatory and pro-degenerative as the disease progresses [195–198]. Notably, DAM microglia increase with ALS disease progression in humans and mice [87,199–201]. Due to DAM formation and function being tightly coupled to TREM2 [125–131], TREM2 has become a potential therapeutic target of interest in hopes of delaying or stopping ALS disease progression.

Post-mortem human ALS ventral horns display increased *TREM2*, *TYROBP*, and *APOE* mRNA expression [202]. Spatial transcriptomics performed on ventral horns from a SOD1 ALS mouse model suggests increased *Trem2* and *Tyrobp* mRNA expression begins presymptomatically [203]. Further, TREM2 knock-out SOD1 mutant ALS mice have increased homeostatic microglia (identified by *P2ry12*) and reduced pro-inflammatory microglia (identified by *Clec7a*, *Apoe*, *Csf1*) in lumbar spinal cord ventral horns [87]. These results advocate the involvement of TREM2 early in disease pathology and the TREM2-dependent induction of a microglia proinflammatory state in ALS.

Despite these results, recent findings propose that TREM2 functions in a neuroprotective manner in ALS. Mislocalization, misfolding, and aggregation of TDP-43 contribute to ALS progression [204–206], and TREM2 knockout mice that had AAV-induced overexpression of human TDP-43 (hTDP-43) resulted in increased aggregation and reduced clearance of TDP-43, leading to more rapid disease progression and exacerbated loss of motor function compared to wild-type controls [52]. TDP-43 is a known ligand of TREM2 [52,53]. Thus, without TREM2, microglia fail to respond to the presence of TDP-43, and exert what appear to be a beneficial role of TREM2 in ALS pathology (**Figure 1**).

8. Spinal Cord Injury

Spinal cord injuries commonly result in incomplete damage with spared tissue, allowing some transmission of signals and partial recovery of function [207–210]. Whether lesions are complete or include spared tissue, there are transcriptional and neuronal circuitry changes outside the lesion zone that contribute to broader effects not strictly localized to the lesion zone or a particular spinal cord area. Another important property is the site of the lesion (cervical, thoracic, lumbar), each impairing different regions of the body. Moreover, spinal cord injuries can result from contusions ("bruising" from blunt force trauma), compression (prolonged pressure on the spinal cord), distension (stretching of the spinal cord), dislocation (shifting of the spinal cord due to dislocated vertebrae), or laceration/transection (cutting of the spinal cord) [211]. Depending on the severity, type, and location of the injury, spinal cord injuries can result in different levels of sensory, motor, and autonomic disturbances. In terms of spinal reflexes involving skeletal muscle specifically, spinal shock occurs immediately following injury, where reflexive circuitry below the injury is temporarily lost or diminished [212–214]. The greater the severity of the injury, the more pronounced and increased duration of spinal shock occurs. Over time, reflexive circuitry below the injury location often returns, frequently resulting in hyperreflexia even if deficits in ascending sensory transmission and descending motor commands persist [213].

The pathophysiology of spinal cord injury is two-part, where the physical damage results in the primary injury, which may be followed by a secondary damage resulting from neuroinflammation, demyelination, excitotoxicity, scarring, apoptosis, as well as whole-body complications (e.g., immunosuppression, neuroendocrine dysfunction, and [221–229gastroesophageal reflux disease) [215–220]. Following spinal cord injury, microglia govern many cellular responses and thereby promote or hinder functional recovery [221,222]. Numerous reviews have covered microglia function following spinal cord injuries, which will not be repeated in detail here [221–229]. They suggest microglia involvement in the formation of the glial scar, the recruitment of peripheral macrophages, phagocytosis of debris, neuronal plasticity, changes to the Blood-Brain Barrier (BBB), and broadly, tissue inflammation. We will focus on the potential roles played by microglial TREM2, which has become increasingly investigated recently.

Microglia are necessary for coordinating initial injury responses and infiltration of peripheral macrophages following mouse T9 dorsal contusion spinal cord injuries [221]. PLX5622-induced microglial depletion before spinal cord injury resulted in: 1) reduced astrocyte and NG2 cell (polydendrocyte) proliferation, which contributed to poor glial scar formation around the lesion core, 2) reduced peripheral macrophage infiltration, 3) diffusion of foamy macrophages that successfully infiltrated into spared white matter region outside of the lesion core, and 4) altered transcription and phenotypes of both infiltrating peripheral macrophages and activated astrocytes which lead to reduced inflammatory gene upregulation, lipid processing, cell adhesion, and proliferation. These changes exacerbated myelin and axon pathology and resulted in increased locomotor deficits/instability 14-35 days post-injury compared to non-depleted animals. *Trem2* and *Syk* mRNA expressions were increased following spinal cord injury and were dependent on microglia activation. *Trem2* specifically was suggested to be involved in governing phagocytosis, endocytosis, and cytokine response, whereas *Syk* was suggested to be involved in the functions mentioned above, as well as protein secretion and cytokine production [221]. This work led Zhao et al. (2025) to investigate the role of TREM2 specifically, after a T9 dorsal contusion injury model [230]. *Trem2* expression increases from one to seven days post-injury and is positively correlated with genes that regulate lysosome membrane permeabilization and phagocytosis, including *Cd68*. In wild-type animals, TREM2 is frequently found near the lesion border, similarly to LAMP1 (Lysosome Associated Membrane Protein 1), a marker of autophagy. Surprisingly, RNA sequencing suggested improved autophagy and lysosomal pathways in TREM2 GKO mice compared to wild-type mice following spinal cord injury [230]. By silencing *Trem2* in BV2 cells (a murine microglia cell line) with an siRNA in vitro, the authors suggest that TREM2 improves microglial autophagy by reducing lysosome membrane permeability and thus improving microglia mitochondrial metabolism. These results

were confirmed in vivo in TREM2 GKO mice seven days post-injury [230]. Zhao et al. (2025) confirmed Brennan et al. (2022)'s results that TREM2 GKO reduces glial scar formation. However, contrary to Brennan et al.'s microglia depletion results, which caused exacerbated locomotor deficits, Zhao et al. found that TREM2-deficient mice demonstrated improved hindlimb motor evoked potentials and hindlimb gait kinematics compared to wild-type mice 35 days post-injury [221,230]. This may suggest that microglial TREM2 may be detrimental for functional recovery. Both studies were performed in a TREM2 GKO mouse model and, therefore, are unable to decouple potential TREM2 functions in microglia or infiltrating peripheral immune cells. Studies in microglia-specific cKO mice, or by pharmacologically altering TREM2 activity in a temporally specific manner, are necessary for decoupling peripheral versus central and early versus delayed TREM2 involvement.

Gao et al. (2023) compared TREM2 GKO to Cx3cr1^{CreER};Trem2$^{flx/flx}$ cKO mice that focused *trem2* deletions to postnatal microglia and reported similar results as Zhao et al. (2025) in both models: improved locomotor function seven days post-injury. Intriguingly, at 28 days post-injury, only GKO mice had reduced lesion size and axon degeneration [78]. The authors suggest that this may indicate that TREM2+ infiltrating peripheral immune cells may have a greater contribution to detrimental outcomes; however, many peripheral macrophages are also CX3CR1+, meaning they also lack *Trem2* in the cKO [231–233]. Intriguingly, single-cell RNA sequencing of both knockout models revealed an increase in perivascular macrophages, suggesting potential alterations at the BBB. No difference in the total number of infiltrating immune cells was observed in both knockout models compared to wild-types, suggesting that TREM2 is not directly involved in peripheral immune cell recruitment. TREM2 knockout myeloid cells had reduced gene expression associated with phagocytosis and lysosomes, assessed by CD68 expression around the lesions [78]. Collectively, these results suggest that TREM2 activity may interfere with functional recovery following spinal cord injury, although improved methodology for temporal and cell-specific regulation of *Trem2* is needed to confirm this conclusion (**Figure 1**).

9. TREM2 Along Peripheral Axons

9.1. Anatomical Overview of Peripheral Nerves

Peripheral nerves may contain motor, sensory, and autonomic axons in variable proportions. All spinal nerves are considered mixed nerves. A single nerve fiber may consist of multiple unmyelinated axons surrounded by the same Schwann cell, or a single myelinated axon with its own Schwann cells. Nerve fibers and their associated Schwann cells are surrounded by an endoneurium. Multiple nerve fibers are further grouped into fascicles and surrounded by the perineurium. The epineurium further bundles multiple fascicles together to form the nerve. The vasa nervorum is the network of blood vessels that run throughout the nerve and may contain infiltrating immune cells [234–238]. Resident and infiltrating immune cells (including macrophages), fibroblasts, perineural cells, pericytes, and endothelial cells can all be found within the nerve as well [239–242]. Disruption of peripheral nerve function directly inhibits the transmission between the CNS and the periphery. Identification of mechanisms to promote recovery or prevent degeneration in aging, disease, and following injury is crucial for maintaining proper circuitry function, and therefore, organismal function. Below we discuss the implications of TREM2 in Schwann cells and peripheral macrophages along peripheral nerves.

9.2. TREM2 in Schwann Cells

Recently, Zhang et al. (2024) published novel evidence that Schwann Cells also express TREM2. By utilizing lentiviral TREM2 knockdown in murine Schwann cell primary culture, Zhang et al. demonstrate that TREM2 deficiency results in impaired PI3K-AKT-mTOR signaling, and activated AMPK and caspases, culminating in mitochondrial damage, impaired mitochondrial metabolism/glycolytic flux, and ultimately apoptosis in Schwann cells. Furthermore, in a mouse model of Acute Motor Axonal Neuropathy (AMAN), Schwann cell TREM2 deficiency exacerbated

sciatic nerve conduction by preventing myelin debris clearance, increasing Schwann cell apoptosis, and preventing axon regeneration in vivo [24]. Collectively, this is the first evidence of TREM2 function in Schwann cells and involvement in PNS axon regeneration (**Figure 1**). TREM2 axonal-Schwann cell signaling should be further explored in other disease contexts to fully understand its role in Schwann cell neuroimmune and homeostatic signaling.

Schwannomas, for example, are benign tumors formed from Schwann Cells in the CNS or PNS, but most commonly along the vestibular nerve. Around five percent of vestibular schwannomas occur due to a mutation in the *NF2* gene (which encodes Merlin protein) and is highly involved in RAS/Raf/MEK/ERK, PI3K/AKT/mTORC1, and other signaling cascades [243]. The remaining 95% of schwannoma cases are sporadic with unknown causes. The tumor microenvironment around schwannomas is diverse but highly influenced by Tumor-Associated Macrophages (TAMs), as there is a correlation between immune-suppressive TAMs and schwannoma progression [243,244]. Although TREM2 has been minimally investigated in the context of schwannomas specifically, TREM2 is a notorious marker for immune-suppressive TAMs [245,246]. In TREM2 knockout mice with fibrosarcoma tumors, the tumor microenvironment was altered to allow increased infiltrating T-cells and improved innate tumor control [245]. Fu et al. (2023) also performed computational analysis on publicly available mRNA expression datasets from individuals with sporadic vestibular schwannomas, which suggested increased TREM2 expression correlated with infiltration of immune cells in human vestibular schwannomas [247]. It is currently unknown if TREM2 mutations are a risk factor for sporadic schwannomas despite utilizing similar downstream signaling cascades, nor if TREM2 in TAMs is involved in schwannoma progression. Collectively, however, the discussed results suggest TREM2 as a potential therapeutic target for peripheral schwannomas and may be translatable to other types of peripheral nerve tumors, which warrants investigation.

9.3. TREM2 in Peripheral Macrophages

Injury-induced axotomy of peripheral axons results in nerve fiber breakdown distal to the injury, following a process known as Wallerian Degeneration. In 1969, Olsson and Sjöstrand demonstrated that macrophages rapidly invade the nerve at the injury location and along the distal stump that is undergoing Wallerian Degeneration [248]. These macrophages provide evidence of phagocytosis as early as three days post-injury, progressively becoming "foamy" macrophages, consistent with lipid metabolism from myelin and axonal debris [242,249,250]. We now know these macrophages also utilize VEGFA-dependent mechanisms to promote angiogenesis and form vascular bridges between proximal and distal nerve stumps, allowing proliferating Schwann cells to bridge the gap and guide regenerating axons to their targets [248,251–257]. Within peripheral nerves, both PNS-resident macrophages as well as infiltrating monocyte-derived macrophages have been identified post-injury. PNS-resident macrophages are suggested to be "microglia-like" as they self-proliferate and have similar transcriptional profiles as microglia (both expressing *Tmem119*, *P2ry12*, *Siglech*, *Trem2*, and *Olfml3*), which are significantly different than infiltrating monocyte-derived macrophages and DRG resident macrophages. Surprisingly, phagocytic bead assay experiments suggest surveying PNS-resident macrophages in the sciatic nerve have greater baseline phagocytic capacity than surveying microglia in spinal cords, potentially suggesting more rapid response capabilities [241,242]. Intriguingly, following nerve injury, GO terms for PNS-resident macrophages specifically suggest involvement with angiogenesis, collagen fibril organization, nerve organization, and axon guidance [241,242]. It remains to be elucidated whether PNS-resident macrophages are the specific subtype of cells responsible for crucial angiogenic bridging between nerve stumps. Following sciatic nerve injury, RNA sequencing experiments have revealed that foamy PNS-resident macrophages display elevated *Trem2*, *Cd68, Arg1*, and *App1* [242,257], suggesting this subpopulation is greatly involved in lipid metabolism and leans toward an immunosuppressive response [242]. Collectively, it's plausible that PNS-resident macrophages may utilize TREM2 to rapidly detect damaged axons, engulf myelin debris, aid in initiating angiogenesis to promote nerve stump bridging, and ultimately resolve

inflammatory responses over time. Based on this literature, we postulate that TREM2 in PNS macrophages may be beneficial following axotomy.

The involvement of PNS macrophages in other neuropathies is a currently developing field of study. In mutant SOD1 ALS rodent models, macrophages infiltrate the peripheral nerve in the pre-symptomatic stage, become foamy, and are filled with mutant SOD1 [258–261]. This finding was confirmed in humans with sporadic ALS [262]. It is generally accepted that peripheral nerve inflammation is not the cause of ALS, but instead a response to early disease changes. However, peripheral macrophages can significantly impact disease progression, as modifying peripheral macrophages to be anti-inflammatory reduces CNS microgliosis, transcriptionally alters microglia to be more "supportive," and extends the life span of ALS mice [262]. The role of PNS-resident macrophages along peripheral axons in the context of Guillian-Barré syndrome, Chronic Inflammatory Demyelinating Polyradiculoneuropathy, Diabetic Polyneuropathy, Chemotherapy-induced peripheral neuropathy, and Charcot-Marie-Tooth Disease was recently reviewed by Msheik et al. [263]. Generally, it is agreed that the microenvironment around PNS resident macrophages greatly shapes their response and function, which can make it difficult when analyzing PNS-resident macrophages in different nerves, organisms, or neuropathies. However, the finding that modulating peripheral macrophages can alter CNS microglia response and disease prognosis makes it a therapeutic target regardless of being beneficial or detrimental. Whether TREM2 in PNS-resident macrophages contributes to the heterogeneity of immune response across neuropathies is currently understudied.

10. TREM2 in Muscle

10.1. Anatomical Overview of Skeletal Muscle

Skeletal muscle not only functions to allow organismal movement and postural control, but also houses proprioceptive receptors, which provide a sense of spatial self-awareness and function to prevent muscle injury. A single muscle is covered by a connective tissue layer called the epimysium. The perimysium further divides the muscle into bundles, which allows vasculature and nerves to run through the body of the muscle [264,265]. Ia and II sensory afferents wrap around intrafusal muscle fibers in muscle spindles surrounded by a fibrous muscle capsule [266–268]. β- and γ-motoneuron innervation of intrafusal fibers control the sensitivity of the muscle spindle and helps regulate muscle tone [269]. Extrafusal muscle fibers, located outside the muscle capsule, are innervated by α- and β-motoneurons, generally accepted to be force-generating during organismal movement [270,271]. The location at which a motoneuron synapses onto muscle fibers is called the Neuromuscular Junction (NMJ). Here, a motoneuron's axon terminal aligns with a muscle's postsynaptic region, characterized by multiple post-junctional folds. The motor axon releases acetylcholine, which binds to muscle nicotinic acetylcholine receptors causing a muscle action potential that ultimately triggers muscle contraction [264,265]. Terminal Schwann cells are a non-myelinating glial cell that encases the NMJ and function to provide structural support, neurotrophic support, neurotransmission regulation, and aid in synapse remodeling during development and reinnervation following injury [272–275]. In addition to neurons and Schwann cells, satellite glial cells, infiltrating immune cells (including infiltrating macrophages), pericytes, endothelial cells, fibro-adipogenic progenitors, adipocytes, fibroblasts, and smooth muscle cells can all be found in skeletal muscle [276–279].

10.2. Overview of Neuromuscular Junction Denervation/Reinnervation

Following a peripheral nerve injury, Wallerian Degeneration occurs, which includes degeneration of the axon terminal and, therefore, denervation from the muscle. Peripheral macrophages and terminal Schwann cells aid in the removal of myelin and neuronal debris. Despite denervation, the post-junctional receptors along the NMJ remain intact, being anchored to basal laminae and covered by terminal Schwann cells [280]. Terminal Schwann cells have been shown to extend processes to neighboring intact NMJ's to aid in motor axon sprouting and reinnervation of

the denervated synapse, while recruiting immune cells to the NMJ through the release of cytokines [256,281]. With increasing time of denervation, the area of terminal Schwann cell coverage declines, accompanied by a loss of post-synaptic acetylcholine receptors and NMJ fragmentation [280–282]. Upon axon regeneration, once the axon has reached its target muscle, terminal Schwann cells aid in guiding the regenerating axon to/through the denervated NMJ [283]. Currently, it is unknown if terminal Schwann cells express TREM2 like the myelinating Schwann cells along peripheral axons. If either infiltrating peripheral macrophages or terminal Schwann cells near the NMJ utilize TREM2 to aid in promoting muscle reinnervation, TREM2 may be used as a therapeutic target for increased functional recovery following peripheral nerve injury, or to aid in conditions such as ALS, where muscle reinnervation does not normally occur.

10.3. TREM2 and the Neuromuscular Junction

TREM2+ macrophages have been identified in aged, diseased, and injured skeletal muscle tissue [284–286], but to date, are more often associated with muscle fiber health rather than NMJ mechanisms specifically. RNA sequencing analysis on human muscle tissue identified a subset of Lipid-Associated Macrophages only present in aged tissue that had elevated *TREM2* expression and enriched GO terms for phagocytosis and lipid metabolism processes. These cells also had elevated *SPP1* (Osteopontin/Secreted Phosphoprotein 1) expression, which is known to promote fibrosis, suggesting this macrophage subtype may be involved in age-related muscle decline [284]. In a mouse model of volumetric muscle loss with persistent inflammation, spatial transcriptomics identified "Scar-Associated Macrophages" with high *Trem2* and *Spp1* levels as the main driver of persistent inflammation and fibrosis [285]. However, the specific ligands and role of TREM2 in the macrophage's response to injury were not identified. Recent literature suggests a protective role of TREM2 in skeletal muscle homeostasis, as mutant TREM2 results in altered skeletal muscle composition and strength in mice [287]. Along these lines, Tacconi et al. (2025) published a novel in vitro study illustrating that bone-marrow derived macrophages acquire a Lipid-Associated Macrophage/TREM2+ phenotype following exposure to palmitate and oleate (1:2, "FFA"). These TREM2+ macrophages consume and store the lipids, suggesting a protective role for their environment, but they also induce transcriptomic changes in neighboring macrophages and skeletal muscles by releasing extracellular vesicles. Extracellular vesicle release subsequently causes increased expression of TREM2 and IL-10 in neighboring macrophages, as well as altered insulin sensitivity, mitochondrial metabolism, and extracellular matrix components in skeletal muscle cells, suggesting tissue remodeling [288]. Collectively, this evidence suggests that TREM2+ macrophages in muscle work to maintain muscle homeostasis but may contribute to fibrosis and muscle alterations with disease or injury.

Despite the current lack of knowledge regarding TREM2 involvement with NMJs specifically, a vast body of literature exists on changes in macrophage activity at the NMJ in injury and disease [256]. The number of macrophages in muscle and their association with the NMJ increase following peripheral nerve injury [256,289] and with ALS disease progression [290,291]. Peripheral nerve injuries performed in mice that lack *Ccr2* have impaired macrophage recruitment to the muscle and diminish muscle function with time, suggesting that infiltrating macrophages are beneficial for muscle reinnervation and functional recovery [289]. In rodent models of SMA, the number of macrophages in muscle dwindles with disease progression. This may indicate a beneficial role for macrophages or simply correlate with the progressive loss of muscle innervation [292]. It is currently unknown if the suggested benefits of infiltrating macrophages into muscle and their association with NMJs in injury or disease involve TREM2 signaling.

11. TREM2 as a Therapeutic Target

We hope we conveyed that TREM2 can have beneficial or detrimental effects depending on the cell type and microenvironment, animal model, age of the organism, kind of disease or injury, and stage of disease or injury. This implies that any TREM2 therapeutics require specificity on cell type,

spatial, *and* temporal targeting. As recently reviewed, TREM2 activity can be modulated via 1) enhancing or blocking TREM2 ligands, 2) introducing agonist or antagonist antibodies, 3) targeting ADAM10/17 to promote or diminish sTREM2, 4) modulating *Trem2* gene expression, or 5) targeting downstream targets (e.g., pSYK) [293]. Several agonist or antagonist TREM2 antibodies capable of crossing the BBB are currently in or have previously been in phase one and two clinical trials [27]. Although many of these antibodies have shown success at modulating microglia and provide some degree of temporal specificity due to antibody half-lives, there is limited research suggesting cell-type or spatial specificity, which may result in off-target and potentially detrimental effects over time. Additional studies should be done on a whole-organismal level and in various disease/injury models to elucidate the efficacy of TREM2 therapeutic antibodies. The utilization of recombinant Adeno-Associated Virus (rAAV) gene therapy to target TREM2 may provide cell type specificity at the cost of temporal controls due to permanent gene editing. New transgenes and viral vectors including temporal controls using clinically approved doxycycline doses will need to be developed [294]. Other current work is being performed to improve rAAV tropism for myeloid cells, such as microglia, which have notoriously been difficult to transfect [295]. PR009 (LY3884965) is a current rAAV gene therapy in Phase 1/2a clinical trials for a rare neurodegenerative disorder, Adult-onset Leukoencephalopathy with axonal Spheroids and Pigmented glia (ALSP), which is caused by mutations in *Csf1r*. PR009 is suggested to increase *TREM2* expression in microglia and, therefore, may be a potential therapeutic intervention for other neurodegenerative conditions with *TREM2* mutation risk factors [296]. Further, PR009 may be a valuable tool for pre-clinical research to decouple central versus peripheral implications of *TREM2* in conditions such as ALS, spinal cord injury, and peripheral nerve injury. By having cell type, spatial, and temporal specificity of TREM2 targeting, the field may finally unravel the complexity of TREM2's implication throughout the body in health, aging, disease, and injury.

12. Concluding Remarks

Functioning neuronal circuitry between the spinal cord and the periphery is crucial for movement, sensation, autonomic function, and the ability to respond to one's environment. Aging, injury, and disease all have different implications on spinal reflex circuitry, but all present with neuroinflammation. TREM2 is an immune-modulatory receptor found in myeloid cells in both the CNS and PNS, and more specifically along all anatomical regions of spinal reflex circuitry. Depending on cell type, microenvironment, age, and type of disease or injury, TREM2 can be beneficial or detrimental (**Figure 1**). Due to the complexities of TREM2 on a whole-organismal level, the development of cell-type, spatial, and temporal specificity for visualizing and modulating TREM2 activity is crucial for pre-clinical research to unravel CNS versus PNS TREM2 effects on health, aging, disease, and injury, and imperative for the development of efficient therapeutic advances with minimal off-target effects.

Abbreviations

5XFAD	5 familial Alzheimer's disease mutations
aa	Amino acid
AD	Alzheimer's disease
ADAM10	A Disintegrin and Metalloproteinase domain-containing protein 10
ADAM17	A Disintegrin and Metalloproteinase domain-containing protein 17
ADI-R	Autism Diagnostic Interview-Revised
AKT	Protein kinase B
ALS	Amyotrophic Lateral Sclerosis
ALSP	Adult-onset Leukoencephalopathy with axonal Spheroids and Pigmented glia
AMAN	Acute Motor Axonal Neuropathy
AMPK	AMP-activated protein kinase
APOE	Apolipoprotein E
app1	Antiphagocytic Protein 1
arg1	Arginase 1
BBB	Blood Brain Barrier
C1q	Complement Component 1q
CCL21	CC chemokine ligand 21/6Ckine
ccr2	Chemokine (C-C motif) Receptor 2
CKO	Conditional Knockout
Clec7a	C-type lectin domain family 7, member A.
CNS	Central Nervous System
CSF1	Colony Stimulating Factor 1
CSF1-R	Colony Stimulating Factor 1 Receptro
CTSD	Cathepsin D
CX3CL1	Fractalkine
CX3CR1	C-X3-C motif chemokine receptor 1/Fractalkine receptor
DAM	Disease Associate Microglia
DAP10/Hcst	DNAX activating protein of 10 KD
DAP12/tryobp	DNAX activating protein of 12 KD
DRG	Dorsal Root Ganglion
ePtdSer	Externalized Phosphatidylserine
ERK	Extracellular Signal-Regulated Kinase
GKO	Global Knockout
IL-10	Interleukin-10
IL-1β	Interleukin -1 β
IL-34	Interleukin-34
IL-6	Interleukin-6
ITAM	Immunoreceptor Tyrosine-based Activation Motif.
KV2.1	Potassium Voltage-Gated Channel, Shab-Related Subfamily, Member 1.
LAMP1	Lysosome Associated Membrane Protein 1
LPL	Lipoprotein Lipase
LPS	lysophosphatidylcholine
MAPK	Mitogen Actived Protein Kinaseitogen A
MEK	mitogen-activated protein kinase kinase
MND	Motor Neuron Disease
mTOR	mechanistic target of rapamycin/mammalian target of rapamycin
NF-κB	Nuclear Factor kappa-light-chain enhancer of activated B cells
NF2	Merline
NMJ	Neuromuscular Junction
olfml3	Olfactomedin-like 3
P2RX4	P2X purinoceptor 4
P2RY12	Purinergic Receptor P2Y, G Protein Coupled, 12
PD	Parkinson's disease
PI3K	Phosphatidylinositol 3-kinase.
PLCγ	Phospholipase C
PNS	Peripheral Nervous Sysyem
PtdSer	Phosphatidylserine

PYK2	Proline-rich tyrosine kinase 2
Raf	Rapidly Accelerated Fibrosarcoma
RAS	Reticular Activating System
RNA	ribonucleic acid
SHIP1	Src homology 2 (SH2) domain-containing inositol polyphosphate 5-phosphatase 1.
SMA	Spinal Muscular Atrophy
SOD1	Superoxide Dismutase 1.
spp1	Secreted Phosphoprotein 1.
sTREM2	Soluble Triggering Receptor Expressed on Myelioid Cells 2
STZ	streptozotocin
SYK	Spleen tyrosine kinase
TAMS	Tumor Associated Macrophages
TDP-43	TAR DNA-binding protein 43
TGF-β	Transforming Growth Factor beta
Tmem119	Transmembrane protein 119
TNFα	Tumor Necrosis Factor-alpha
TREM2	Triggering Receptor Expressed on Myeloid Cells 2
VAV2/3	Vav family of guanine nucleotide exchange factors 2/3
VEGFA	Vascular Endothelial Growth Factor A

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