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Review

Targeting of Tumor Necrosis Factor Alpha Receptors as a Therapeutic Strategy for Neurodegenerative Disorders

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Abstract: Numerous studies have revealed the pleiotropic functions of tumor necrosis factor alpha (TNF-α), and have linked it with several neurodegenerative disorders. This review describes the signaling pathways induced by TNF-α via its two receptors (TNFR1 and TNFR2), and their functions in neurodegenerative processes as in Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and ischemic stroke. It has become clear that TNF-α may exert divergent actions in neurodegenerative disorders, including neurodegenerative and neuroprotective effects, which appear to depend on its signaling via either TNFR1 or TNFR2. Specific targeting of these receptors is a promising therapeutic strategy for many disorders.

1. Introduction

Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine implicated in multiple inflammatory diseases, including cancer, rheumatoid arthritis, and in neurodegeneration as in Alzheimer's disease (AD), stroke, multiple sclerosis (MS), and Parkinson's disease (PD) [1–5]. TNF-α is synthesized as a type II transmembrane protein of 26 kDa and forms a stable homo-trimeric molecule (mTNF-α) to exert its pleiotropic biological activities. It can be processed by proteolytic cleavage via TNF-α converting enzyme (TACE/ADAM17) to a 17 kDa monomeric protein, which is biologically active as a soluble homo-trimeric molecule of 51 kDa (sTNF-α). TNF-α induces various cellular responses through its interaction with two distinct transmembrane receptors, the 55 kDa TNF receptor type I (TNFR1) and the 75 kDa TNF receptor type II (TNFR2). Under normal physiological conditions, TNFR1 is ubiquitously expressed in various cell types and tissues, whereas TNFR2 is predominantly expressed at low levels in immune cells and endothelial cells [6–9]. TNFR1 activation can be induced by either sTNF-α or mTNF-α, and TNFR2 activation is predominantly initiated by mTNF-α [10]. TNF-α is classically known to exert pro-apoptotic functions via TNFR1 [11] and via TNFR2 in co-operation with TNFR1 [12,13]. On the contrary, more recent evidence clearly indicates that TNF-α induces cell survival and cellular proliferation via its TNFR2 [14,15]. This led to new insights that TNF-α exerts opposing effects via its two receptors with respect to neurodegeneration and neuroprotection. The potent pro-inflammatory functions of TNF-α in the brain play an important role in the etiology of neurodegenerative disorders such as ischemia/ischemic stroke, MS, and AD [14,16–18]. Therefore, a thorough understanding of TNF-α signaling pathways in neurodegenerative disorders can promote the development of effective agents in the treatment of these conditions.

This review will discuss TNF-α-mediated functions in the healthy and unhealthy central nervous system (CNS), focusing on TNF-α-mediated signaling pathways via its receptors, TNFR1 and TNFR2. Finally, we will examine these signaling pathways as potential therapeutic strategies for neurodegenerative disorders, focusing on AD, PD, ischemic stroke, and MS.

2. TNF-α Receptor Signaling Pathways

2.1. TNF-α Receptor 1 Signaling

The two distinct transmembrane receptors of TNF-α are characterized by a conserved domain of N-terminal repeating cysteine-rich motif in extracellular regions that specifically interact with diverse TNF-related ligands [19]. The conserved domain is necessary and sufficient for the preassembly of TNFR complexes that bind TNF-α trimers and mediate downstream signaling [20]. However, the intracellular domains of the two receptors lack homologous sequences [21], suggesting that distinct signaling pathways emanate from the two receptors. TNFR1 is distinguished from TNFR2 by its intracellular death domains (DDs) [22]. The extracellular domain of TNFR1 contains a well-ordered

cysteine-rich amino-terminal, known as the preligand binding assembly domain (PLAD). PLAD favors pre-assembly of TNFR1 into trimeric complexes and functions as a preventative measure for receptor auto-activation and is essential for ligand binding [23]. TNFR1 can be activated by both sTNF-α and mTNF-α [10]. TNFR1-induced apoptosis involves formations of two sequential signal complexes (complex I and complex II) that are separated both temporally and spatially, but is limited by the successful activation of complex I [24]. After TNF-α binding, the activated TNFR1 acts via its intracellular DDs to recruit the core adaptor TNFR-associated death domain (TRADD) [25–27]. Furthermore, receptor-interacting protein 1 (RIP1) is recruited rapidly and modified with non-degradative poly-ubiquitin chains [28,29]. TRADD subsequently recruits other proteins such as TNFR-associated factor 2 (TRAF2) [30], inhibitor of apoptosis protein 1 (cIAP1), and inhibitor of apoptosis protein 2 (cIAP2) [31], forming the initial signaling complex I. This signaling complex with RIP1 ubiquitination initiates the later activation of the catalytic IκB kinase (IKK) complex [32]. The activated IKK complex, which consists of an IKKα subunit and an IKKβ subunit, functions as an essential regulatory subunit of the IKK complex (IKKγ/NEMO), which subsequently phosphorylates the inhibitor of the kappa-B (IκB) complex [33]. The IκB complex is then degraded via the ubiquitin-proteasome. Consequently, NF-κB composed of p50/p52 and RelA (p65)/RelB subunits is released and translocated into the nucleus to initiate the transcription of anti-apoptotic genes, cIAP-1, cIAP-2, TRAF1, TFAF2 as well as cellular FLICE-like inhibitory protein (cFLIP), to inhibit caspase 8 release from complex II [30,32,34–36] (Figure 1). The caspase-8 inhibitor cFLIP(L), which is harbored in complex II, simultaneously inhibits the release of pre-caspase 8 [24,34].

When complex I signaling fails to activate the NF-κB pathway in some instances, the activated TNFR1 will recruit complex II to trigger apoptotic processing (Figure 1). After ligand binding to TNFR1, the silencer of DDs is dissociated from the intracellular domains of TNFR1, and recruits the adaptor proteins such as TRADD, RIP1, TRAF2, and Fas-associated death domain (FADD) and pre-caspase 8 to form complex II [35]. In the activated complex, FADD triggers pre-caspase 8 activation, resulting in the release of p18/p12 fragments that can trigger downstream caspase cascades to participate in apoptotic processes [24]. This pro-apoptotic signaling mechanism involves FADD and caspase 8 as the key factors to trigger apoptosis [36,37]. Upon recruitment of FADD and caspase-8, initiation of apoptosis via caspase-8 is mainly determined by levels of the anti-apoptotic protein cFLIP(L) [38]. NF-κB activation triggered by complex I signaling determines the availability of the cFLIP(L) protein at the moment complex II is formed [38]. Therefore, adequate production of cFLIP(L) via NF-κB upon complex I signaling prevents subsequent caspase-8-mediated apoptosis of the complex II signaling pathway [39].

TNFR1 signaling can also trigger caspase-independent programmed necrosis (necroptosis) in Jurkat cells and in ischemic brain injury [40–42]. It was shown in mouse embryonic TNFR1$^{-/-}$ fibroblast cells that necrotic cell death is primarily dependent on TNFR1-mediated pathways [43]. In this process, RIPs, FADD, and TRAF2 elements are still the critical components to form complex IIb [43] (Figure 1). RIP1 is required for the formation of complex IIb [44]. Additionally, RIP3 assembly is essential for RIP1 recruitment to this complex and is identified as a crucial kinase to phosphorylate RIP1, which in turn phosphorylates RIP3 to form the RIP1-RIP3 pre-necrotic complex [45]. This activated complex phosphorylates the downstream mixed lineage kinase domain-like protein (MLKL) which subsequently triggers necrosis [46]. MLKL is therefore a critical factor in RIP3-mediated downstream necroptotic pathways. Dephosphorylation of RIP3 via protein phosphatase 1B (Ppm1b) restricts necroptosis [47]. In

addition to caspase suppression, cFLIP proteins can potentially inhibit TNF-induced necroptosis [48]. Necroptosis is a newly discovered pathway of cell death with essential functions in tissue homeostasis and development, and is particularly studied in cancers and skin diseases. However, research on this pathway remains rather limited in CNS conditions. In primary hippocampal neurons, necroptosis was induced via RIP3 upon an ischemic insult [49]. Moreover, it was recently shown *in vivo* in mice that intracerebroventricular injection with TNF-α caused RIP3-mediated necroptosis of hippocampal neurons [50]. Besides neurons, necroptosis can also occur in activated (by stimulation with different inflammatory stimuli, including TNF-α) primary microglia upon the inhibition of caspase-8 [51]. Interestingly, in mixed cultures (where also primary neurons and astrocytes were present), necroptosis of activated microglia protected neurons from cell death [51]. Yuan's group [52] reported that necroptosis in cortical neurons mainly depends on the RIP1-RIP3-MLKL signaling pathway induced via TNF-α/TNFR1 in MS. Przedborski's group [53], however, showed that necroptosis-driven death of motor neurons triggered by amyotrophic lateral sclerosis (ALS) involves the RIP1-MLKL signaling pathway independent of TNF signaling. As such, it seems that RIP1-MLKL-mediated neuronal necroptosis may be induced in different ways, both dependent or independent of TNF-α.

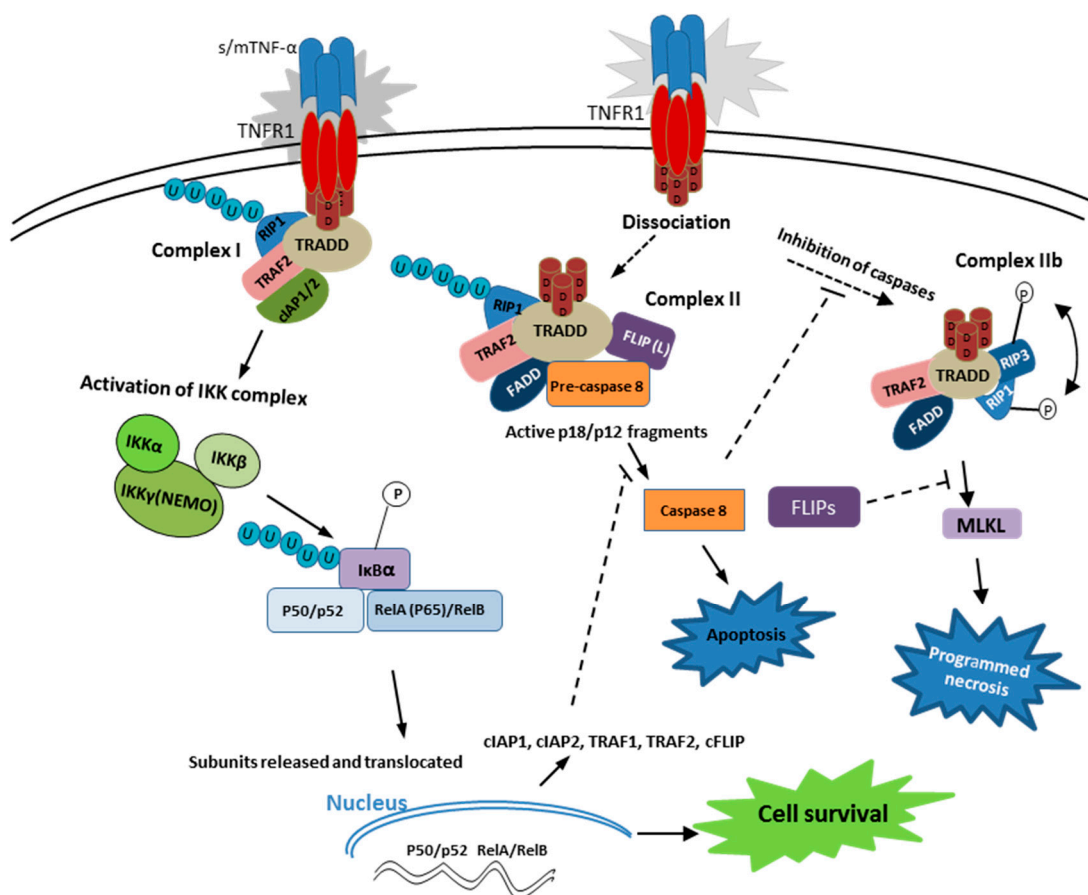**Figure 1.** Multiple forms of TNFR1 signaling activation are mediated through intracellular protein complex assembly. The trimeric TNF-α engagement of TNFR1 leads to cellular apoptosis or cell survival via the distinct complex signaling pathways.

2.2. TNF-α Receptor 2 Signaling

Compared to TNFR1-mediated pathways, TNFR2-mediated signaling is still less well understood. TNFR2 is typically expressed at a low level in cells of the immune system, and is activated primarily by mTNF-α [10]. Unlike TNFR1, TNFR2 does not include a death domain (DD). Trimerization of TNFR2 is induced upon binding of mTNF-α, leading to the recruitment of TRAF2 to the intracellular TRAF binding motif, which subsequently causes the recruitments of TRAF1, cIAP1, and cIAP2 [54] (Figure 2). TRAF2 is a key mediator in this signaling pathway that triggers the subsequent signaling cascades leading to activation of NF-κB [55]. The activation TRAF2-cIAP1/2 complex is recruited to NF-κB-inducing kinase (NIK) by TRAF3, resulting in proteosomal degradation of NIK [56]. TNFR2 activation by mTNF-α maintains NIK stabilization via induction of TRAF3 degradation, and thereby activates IκBα, leading to phosphorylation and activation of IKKα. Phosphorylated IKKα consequently activates the NF-κB precursor protein p100 [57]. This noncanonical NF-κB activation is independent of IKKβ and IKKγ [56]. Moreover, it has been reported that human TNFR2 contains a second intracellular binding region for TRAF2 and that this intracellular region can recruit TRAF2, which leads to the activation of NF-κB, dependent on activation of NIK and IκBα. Deletion of this binding region impairs the ability of TNFR2 to activate NF-κB [58].

TNFR2-mediated activation of NF-κB can also occur via the phosphoinositide 3-kinases (PI3K)-protein kinase B/serine-threonine kinase (PKB/Akt) signaling pathway [59] (Figure 2). The phosphorylated IκB is degraded via the ubiquitin-proteasome and NF-κB is translocated into the nucleus to initiate transcription [60]. TNFR2-mediated NF-κB activation is downregulated by phosphatase and the tensin homolog deleted on chromosome 10 (PTEN), which is a strong inhibitor of the PI3K-PKB/Akt pathway. However, NF-κB activation via TNF-α leads to downregulation of PTEN [61].

In addition to NF-κB activation, signaling via TNFR2 can elicit various non-apoptotic responses including c-Jun N-terminal kinase (JNK) or p38 mitogen-activated protein kinases (MAPK) that depend on the recruitment of TRAF2 to the different intracellular binding sites of TNFR2 [54,62]. In these signaling pathways, TNFR2 binds TRAF2 to its intracellular region, and subsequently recruits TRAF1, TRAF3, cIAP1, and cIAP2 [63,64]. According to spatial and temporal separation, this complex binds to a MAPK kinase kinase (MAP3K) protein called MEKK1 and enhances the activity of this kinase and the phosphorylation of JNK-activating kinase (JNKK1) [65], and thereby stimulates JNK activation to promote downstream signaling pathways which mediate cell survival. It should be noted, however, that while acute activation of JNK via TRAF2 has been related to cell survival, prolonged activation may also lead to apoptosis [66–68]. TNF-α-mediated JNK activation depends at least in part on MEKK1 [62,65]. As opposed to TRAF1 and TRAF3, TRAF2 positively regulates JNK activation [55]. It has been suggested that TNFR2 harbors two sequences that are adaptors specific for JNK signaling [69]. TNFR2-TRAFs/cIAPs can mediate activation of the p38 MAPK signaling pathway. TRAF2 is a major player to promote activation of the p38 MAPK signaling pathway [70]. In this pathway, the TRAFs/cIAPs complex recruits RIP and subsequently activates MKK3 to initiate p38 MAPK activation [27,71,72].

TRAF2, TRAF1, and cIAP play a pivotal role not only in TNFR1 signaling pathways but also in TNFR2 pathways. This implicates that there could be a crosstalk between the two receptors [73]. It has been demonstrated that the depletion of TRAF2 induced by TNFR2 activation specifically accelerates the TNFR1-dependent caspase 8 activation [74–76]. TNFR2 signaling in a certain circumstance may

therefore enhance TNFR1-mediated apoptosis by caspase 8 activation. Crosstalk between TNFR1 and TNFR2 is complicated and dependent on the physiologic environment and signaling kinetics between the two receptors. We have previously described TNFR crosstalk in [73].
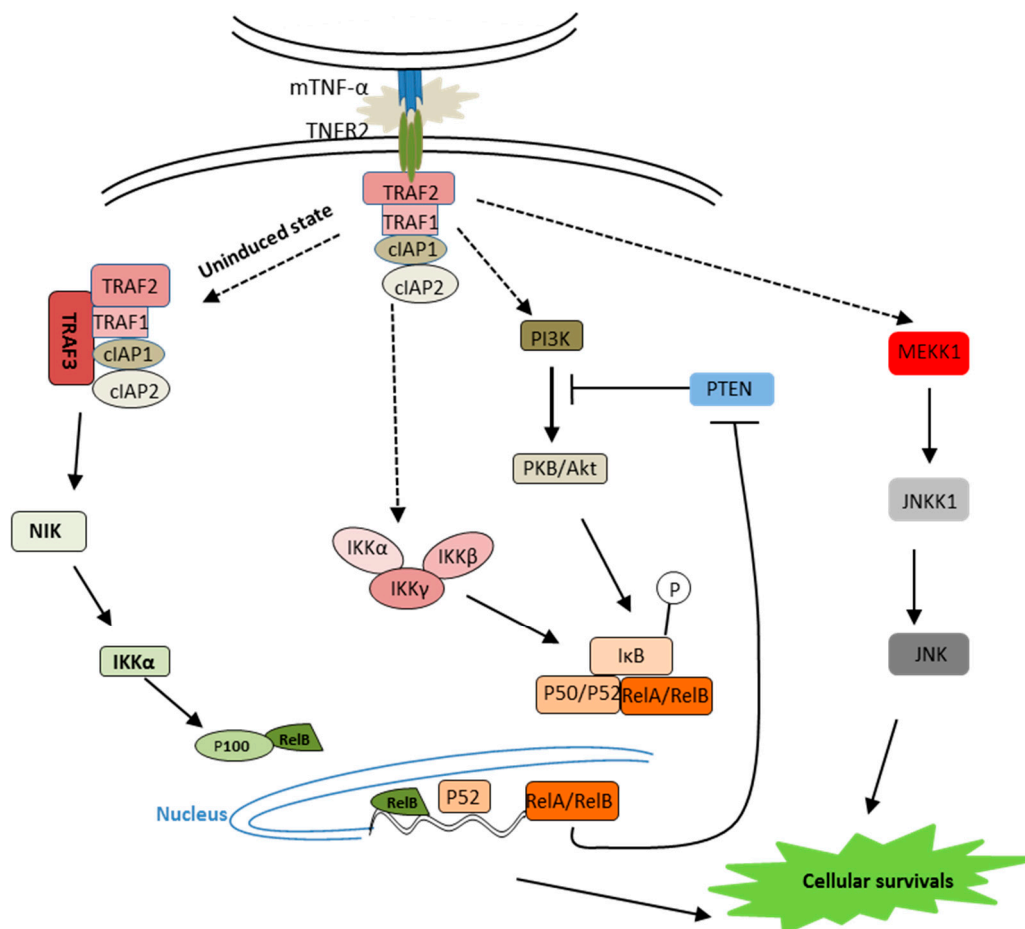
Figure 2. Multiple forms of TNFR2 signaling activation are mediated through intracellular protein complex assembly. The transmembrane trimeric TNF-α engagement of TNFR2 leads to cellular survival via the distinct complex signaling pathways. PKB/Akt signaling is described in [59,73].

3. TNF and Its Receptors—Involvement in Neurodegenerative Disorders

3.1. Alzheimer's Disease

AD is a progressive neurodegenerative disorder, and the most common cause of dementia [77]. Besides the well-known pathological hallmarks of AD, including the formation of toxic aggregates of amyloid beta (Aβ) and hyperphosphorylated tau proteins, neuroinflammation was more recently described to play a fundamental role in the pathophysiological processes of AD, in which TNF-α in particular could be an important mediator [78] (also see Table 1). Evidence for the involvement of TNF-α in AD emanates from various research disciplines. On a genetic level, multiple polymorphisms in the TNF-α gene may be associated with the risk of developing AD [79]. For example, the TNF-α G308A promoter polymorphism, which may cause higher TNF-α expression levels, has been found to increase the risk of AD in certain populations [80–82]. At the protein level, plasma and serum TNF-α protein

levels are elevated in AD [83–85]. Moreover, TNF-α levels in AD brain tissue were found to be increased, originating from microglia surrounding Aβ plaques [86–88]. Besides promoting ongoing pro-inflammatory processes in the AD brain, increased TNF-α levels can also affect the accumulation of Aβ. For example, it has been suggested that higher levels of pro-inflammatory cytokines may interfere with phagocytosis of fibrillar Aβ via mechanisms that need further clarification [89]. Yet, in monocyte-derived macrophages, it was shown that cytokines, including TNF-α, could directly decrease the expression of mediators involved in the degradation of aggregated proteins, such as insulin degrading enzyme, thereby interfering with the breakdown of fibrillary Aβ [90]. Moreover, TNF-α may increase Aβ production by enhancing beta-secretase (BACE1) expression (via NF-κB-dependent pathways) and activity and stimulating gamma-secretase activity via JNK-dependent MAPK signaling [91,92].

The extents of signaling through TNFR1 and TNFR2 are an important aspect to consider when interpreting the role of increased TNF-α in AD. TNFR1 protein levels in human post-mortem AD brain tissue are significantly increased as compared to non-demented age-matched controls, while TNFR2 protein levels are decreased [88,93]. Moreover, it appeared that TNF-α in the AD brain has an increased binding affinity to TNFR1 but a decreased affinity for TNFR2 [94]. Interestingly, Zhao *et al.* also reported significantly increased levels of TRADD and caspase-3 in AD brains [88]. Data from these studies suggest a shift towards TNFR1-mediated signaling in AD. On a genetic level, a polymorphism in exon 6 of the TNFR2 gene is associated with late-onset AD [95]. The functional consequences of this polymorphism in TNFR2, however, remain, to our knowledge, unclear.

Studies using AD mouse models also have aimed to further the understanding of the role of TNF-α receptors in AD pathology. Montgomery *et al.* (2011) found that deletion of both TNFR1 and TNFR2 in triple-transgenic AD mice (3xTg-AD) significantly exacerbated AD pathology [96]. This suggests that total blockage of TNF-α signaling is not beneficial in this condition, and that both TNFRs should be appreciated separately. Interestingly, Montgomery *et al.* (2013) supported this idea by showing that the silencing of TNFR2 aggravates TNFR1-mediated Aβ and tau pathology in aged 3xTg-AD mice [97]. Moreover, knock-down of either TNFR2 or both TNF-α receptors caused enhanced neuroinflammation [97]. Likewise, the group of Shen recently reported that genetic deletion of TNFR2 enhances AD pathology in the APP23 mouse model for AD, while TNFR2 overexpression can reverse these findings [98]. The same group also showed that genetic deletion of TNFR1 resulted in inhibition of Aβ production in APP23 mice, and prevented learning and memory deficits [91]. McAlpine *et al.* showed that the inactivation of TNFR1 signaling diminished Aβ pathology in 3xTgAD mice, and that administration of inhibitors of sTNF-α (which predominantly activates TNFR1) had similar beneficial effects in 3xTgAD mice [99]. Moreover, intracerebroventricular injection of oligomeric Aβ resulted in cognitive decline in wild-type mice, but did not affect cognition in TNFR1 knockout mice [3]. Finally, in an *in vitro* study with the SH-SY5Y neuroblastoma cell line, silencing of TNFR2 aggravated the neurotoxic effect of Aβ [100]. These findings overall seem to support the hypothesis that increased TNFR1 signaling and/or decreased TNFR2 signaling may play an important role in AD pathology.

3.2. Parkinson's Disease

Neuroinflammation—besides the aggregation of alpha-synuclein (α-synuclein) proteins—also plays an important role in PD, by directly or indirectly contributing to the degeneration and death of dopaminergic neurons in the substantia nigra [101,102]. The role of TNF-α and its receptors in PD was

also previously reviewed by McCoy and Tansey (2008) [103]. TNF-α levels are significantly increased in the brain and CSF of PD patients [102,104], and increased TNFR1 levels were found in the substantia nigra of PD patients [105]. Evidence for the involvement of TNF-α and its receptors in mechanisms of PD progression is described in studies with different PD animal models and *in vitro* models (also see Table 1). For example, some models aim to mimic the α-synucleinopathy that is observed in PD by overexpressing wild-type or mutant α-synuclein. *In vitro*, BV2 cells (a murine microglial cell line) showed elevated TNF-α secretion upon α-synuclein overexpression [106], and primary murine microglia presented a significant increase in TNF-α expression after exposure to mutant α-synuclein [107]. *In vivo*, overexpression of α-synuclein via recombinant adeno-associated virus (AAV-synuclein) injection into the substantia nigra was also found to increase TNF-α expression [108,109]. Another PD model makes use of 6-hydroxydopamine (6-OHDA), a toxic dopamine analogue which leads to dopaminergic neuron death upon administration. *In vitro*, it was shown that selective activation of TNFR2 (by TNC-scTNFR2, a TNFR2-specific agonist) rescued cultured neurons from 6-OHDA-induced cell death [110]. *In vivo*, peripheral and intranigral injection in rats with specific inhibitors of sTNF-α (XPro-1595 and XENP345, respectively) was shown to reduce 6-OHDA-induced death of dopamine neurons [111–114]. Considering that sTNF-α preferably binds and activates TNFR1 rather than TNFR2, and that TNFR1 is highly expressed by dopamine neurons, it was suggested that the neuroprotective effects of these sTNF-α blockers may have resulted mostly from attenuated signaling via TNFR1 [112,115]. These findings indicate that TNF-α and its receptors exert similar functions in PD as previously described for AD; TNF-α functioning is shifted towards increased TNFR1 signaling, and certain neuroprotective effects induced via TNFR2 signaling are decreased. It should be noted, however, that studies using mice with TNFR1 and/or TNFR2 deletions have led to contradictory findings about their roles in PD pathology, which may be due to differences in the PD models used, as reviewed in [103]. For example, it was shown that mice lacking both TNFR1 and TNFR2 in the 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP, a dopaminergic neurotoxin) model for PD were completely protected against the dopaminergic neurotoxicity of MPTP, while mice lacking either TNFR1 or TNFR2 were not protected [116].

3.3. Ischemic Stroke

Ischemic stroke can arise when a blood vessel supplying blood to the brain is obstructed. Sudden loss of blood flow to a brain region causes damage and cell death in the (nutrient- and oxygen-) deprived area. Upon ischemic stroke, different brain cell types in proximity of the ischemic lesion site (including neurons, microglia, and astrocytes) increase their production of TNF-α. This has been shown in human brain tissue as well as in experimental animal models of stroke [117–120]. As reviewed by Pan and Kastin (2007), TNF-α was shown to have both detrimental and beneficial effects in stroke [121]. Several studies reported that inhibition of TNF-α (e.g., by etanercept, a human TNFR2-IgG Fc fusion protein) reduces infarct size and neuroinflammation [122–125], while, on the other hand, complete knockout of both TNFRs increases the sensitivity for stroke and aggravates neuronal damage [5]. Moreover, in stroke *in vitro* and animal models, pre-treatment with TNF-α (which models ischemic preconditioning) mediates neuroprotective effects after ischemia [126,127]. In accordance with the above-discussed disorders, complete abolition of TNF-α signaling, as well as exaggerated TNF-α signaling, are detrimental in ischemic stroke. This may likely depend on the contribution of TNF-α/TNFR1 and TNF-α/

TNFR2 signaling (also see Table 1). In addition to TNF-α, its receptors are also upregulated in stroke. In a rat model for stroke by permanent middle cerebral artery occlusion (MCAO), TNFR1 upregulation was apparent after 6 h, while TNFR2 upregulation followed at 24 h [121,128]. Time differences in upregulation of TNFR1 and TNFR2 expression can be explained by studies showing that TNFR1 expression is mainly regulated by post-translational processes, while TNFR2 is believed to be controlled by transcriptional factors such as NF-κB [129–131]. Studies investigating the effects of TNFR1- and TNFR2-mediated signaling in ischemia and stroke have resulted in contrasting findings. For example, it was shown by Gary *et al.* (1998) that the infarct size in mice after MCAO is significantly larger in TNFR1 knockout mice than in wild-type or TNFR2 knockout mice [132]. Lambertsen *et al.* similarly showed larger infarct sizes in TNFR1 knockout mice compared with wild-type and TNFR2 knockout mice in a focal cerebral ischemia model [133]. Moreover, TNFR1 was implicated in ischemic preconditioning, in which a short ischemic event may result in resistance to severe ischemic injury [134]. It was shown that ischemic preconditioning (induced by a 10 min transient MCAO) caused TNFR1 upregulation in neurons, and that this upregulation in TNFR1 expression in ischemic preconditioning was associated with a smaller infarct size [134]. Taoufik *et al.* reported that TNFR1 signaling is responsible for upregulating different neuroprotective mediators, *i.e.*, vascular endothelial growth factor, upon an ischemic lesion in the mouse brain [135,136]. In addition, a study investigating mice deficient of TNFR1 and transgenic for human TNFR2 implicated that TNFR2 signaling induced pro-inflammatory responses in the CNS vasculature, resulting in inflammatory ischemia [137]. These findings imply a neuroprotective role for TNFR1, while TNFR2 signaling may have detrimental effects by aggravating neuroinflammatory processes. However, conflicting data is also present. For example, our group previously showed that absence of TNFR1 in mice strongly reduced neurodegeneration after retinal ischemia-reperfusion, while a lack of TNFR2 exacerbated neurodegeneration [16]. This finding indicates that TNFR1 signaling may augment neuronal death and TNFR2 may promote neuroprotection. In accordance, an *in vitro* study with the SH-SY5Y neuroblastoma cell line showed that silencing of TNFR2 aggravated cell injury upon hypoxic conditions [100]. Moreover, in the immature brain, TNFR1-JNK signaling was responsible for neuroinflammation and neurovascular damage in lipopolysaccharide (LPS)-sensitized hypoxic-ischemia brain injury [138]. The different models of ischemia that were used may, in part, explain these contradictory findings. Furthermore, the duration of the induced ischemia (acute/transient *vs.* chronic) might potentially affect the pathways, kinetics, and outcomes of TNF signaling. Also, the acuteness of ischemic lesions may explain differences between ischemic stroke and other neurodegenerative disorders like AD and PD, which gradually develop over a longer period of time. In disorders that develop slowly, the expression levels and distribution of TNFRs may gradually change during the pathological process (e.g., resulting in lower TNFR2 expression in AD brains). This might explain how acute insults could result in different effects of TNF-α, as compared to conditions in which lesions arise over a longer period of time.

3.4. Multiple Sclerosis

MS is a chronic demyelinating disease of the CNS, resulting in disrupted nerve signaling and therefore a wide range of neurological symptoms. It has been suggested that the demyelination of axons is due to the death of myelin-forming oligodendrocytes, which in part may be caused by detrimental inflammatory

and immune responses targeted to these cells [139]. The involvement of TNF-α in MS has been explored in several studies [103] (also see Table 1). Increased TNF-α levels were found in MS lesions [140,141]. In a transgenic mouse model that overexpresses murine TNF-α specifically in the CNS, it was demonstrated that constitutive TNF-α expression leads to spontaneous development of a chronic inflammatory demyelinating disorder [142]. In addition, peripherally increased TNF-α levels have been associated with synaptic instability in the brain, and as such may contribute to sensory and cognitive impairments as seen in MS [143]. On the other hand, complete knockout of TNF-α in experimental autoimmune encephalomyelitis (EAE, an MS animal model) mice caused deleterious effects, including increased inflammation, demyelination, and higher mortality as compared to control mice [144,145]. In the cuprizone model (a toxin causing reversible demyelination), complete knockout of TNF-α in mice resulted in delayed demyelination (suggesting that TNF-α promotes acute demyelination) as well as delayed remyelination (suggesting that in later stages, TNF-α promotes remyelination) [146]. The beneficial *versus* detrimental effects of TNF-α in MS may greatly depend on its signaling via either TNFR1 or TNFR2. Akassoglou *et al.* (1998) demonstrated a dominant role for TNFR1 signaling in TNF-mediated oligodendrocyte apoptosis and primary demyelination [147]. In addition, TNFR1 was suggested to contribute to inflammatory infiltration of the EAE spinal cord [148]. Interestingly, it was recently shown in different studies that administration of an antagonistic antibody that selectively targets TNFR1 ameliorated disease symptoms in the EAE mouse model [18,149]. Also, inhibition of sTNF-α by XPro-1595 protected EAE mice from clinical symptoms and improved axon preservation and remyelination, indicating a detrimental effect of sTNF-α (which signals mostly via TNFR1) [150,151]. Furthermore, studies showed that TNFR1 knockout mice do not develop EAE, or have a less severe disease course. TNFR2 knockout mice, on the other hand, were seen to develop more extensive demyelination and aggravated EAE disease symptoms [18,152–154]. Similarly, in the cuprizone model, TNFR2 was shown to be responsible for TNF-α mediated remyelination and proliferation of oligodendrocyte precursor cells [146]. A neuroprotective role of TNFR2 on oligodendrocyte progenitor cells was also directly shown in *in vitro* studies by Maier *et al.* (2013) [155]. In this study, primary oligodendrocytes from transgenic mice expressing human TNFR2 were shown to be protected from oxidative stress after preconditioning the cells with a TNFR2 specific agonist. This protective effect might be elicited by TNFR2-mediated induction of anti-apoptotic and cell survival genes [155]. Taking the above results together, it may not be a surprise that general blockage of TNF-α signaling can have a net detrimental effect, by also inhibiting the neuroprotective signaling of TNF-α. This idea is supported by different studies, including a phase II study in which administration of the TNF-α antagonist lenercept was associated with exacerbation of symptoms in MS patients [156], and case reports linking etanercept treatment with the onset of MS [157,158]. In general, specifically blocking TNFR1 or stimulating TNFR2 signaling may provide a promising therapeutic possibility in MS. It should be noted, however, that TNFR1 might also have beneficial effects in MS. For example, it has been suggested that TNFR1 signaling is important for the onset of EAE, but also for limiting EAE progression at a later stage [115]. Therefore, specific modulation of TNF-α receptor-mediated signaling at specific stages of the disease may be a promising approach for effective outcomes in MS.

Table 1. Summary of the TNF-α family members that are subjects of this review, and their roles in neurodegenerative conditions.

Condition	TNF-α family member	Tissue	Finding	Model	Ref.
Alzheimer's disease (AD)	TNF-α	CNS	TNF-α protein levels are increased in AD brain tissue.	Human AD patients.	[86–88]
		Plasma and serum	TNF-α protein levels are increased in AD plasma and serum.	Human AD patients.	[83–85]
	TNFR1 and TNFR2	CNS	TNFR1 protein levels are increased, TNFR2 protein levels are decreased.	Human AD patients.	[88,93]
			Deletion of both TNFRs exacerbates AD pathology.	3xTg-AD mouse model.	[96]
			Silencing or deletion of TNFR2 aggravates AD pathology. TNFR2 overexpression reverses these effects.	3xTg-AD mouse model and APP23 mouse model.	[97]
			In vitro, TNFR2 silencing promotes Aβ neurotoxic effects.	SH-SY5Y cell line.	[100]
			Deletion of TNFR1 diminishes AD pathology.	3xTg-AD mouse model and APP23 mouse model.	[91]
			sTNF-α inhibitors diminish AD pathology.	3xTg-AD mouse model.	[99]
	sTNFR1 and sTNFR2	CSF, serum and plasma	sTNFR1 levels are increased. sTNFR2 levels are unchanged or decreased.	Human control and MCI patients.	[159–163]
			Higher sTNFR1 serum levels can predict conversion from MCI to AD.	Human control and MCI patients.	[161]
			sTNFR1 and sTNFR2 levels correlate with BACE1 activity and Aβ40 levels, as well as with tau CSF levels.	Human control and MCI patients.	[164]
Parkinson's disease (PD)	TNF-α	CNS and CSF	TNF-α levels are increased in brain and CSF.	Human control and PD patients.	[96,98]
			TNF-α levels are increased in brain.	α-Synuclein overexpression cell line and mouse models.	[106]
	TNFR1	CNS	TNFR1 levels are increased in the substantia nigra.	Human control and PD patients.	[105]
			sTNF-α inhibitors reduce cell death of dopamine neurons.	Rat 6-OHDA toxicity model.	[111–114]

Table 1. *Cont.*

Condition	TNF-α family member	Tissue	Finding	Model	Ref.
Parkinson's disease (PD)	TNFR2	CNS	Selective activation of TNFR2 protects dopaminergic neurons.	Neuronal culture, 6-OHDA toxicity model.	[110]
	TNFR1 and TNFR2	CNS	Deletion of both TNFRs protects from dopaminergic toxicity, while lack of either TNFRs alone is not protective.	Mouse, MPTP toxicity model.	[116]
	sTNFR1	Serum and plasma	Serum sTNFR1 levels are increased.	Human control and PD patients.	[102,104, 165]
			Higher serum sTNFR1 correlate with a later onset of sporadic PD.	Human control and PD patients.	[165]
			Elevated plasma sTNFR1 levels predict poorer executive functioning in PD.	Human control and PD patients.	[166]
Ischemic stroke	TNF-α	CNS	TNF-α production is increased around the lesion site.	Human brain tissue and animal models of stroke.	[117–120]
			Inhibition of TNF-α reduces infarct size and neuroinflammation.	Stroke mouse models.	[122–125]
	TNFR1	CNS	TNFR1 knockout mice have larger infarct sizes compared to wild-type and TNFR2 knockout mice.	Stroke mouse model.	[134,135]
			TNFR1 is responsible for expression of neuroprotective factors upon ischemia.	Stroke mouse model.	[135,136]
			Absence of TNFR1 reduces retinal ischemia-reperfusion damage.	Mouse retinal ischemia-reperfusion model.	[16]
			TNFR1 signaling causes neuroinflammation and neurovascular damage in the immature brain.	LPS-sensitized hypoxic-ischemia mouse model.	[138]
	TNFR2	CNS	Absence of TNFR2 aggravates retinal ischemia-reperfusion damage.	Mouse retinal ischemia-reperfusion model.	[16]
			TNFR2 silencing increases cell injury upon hypoxic conditions.	SH-SY5Y cell line.	[100]
			TNFR2 signaling can result in inflammatory ischemia.	Stroke mouse model.	[137]
	TNFR1 and TNFR2	CNS	Deletion of both TNFRs aggravates neuronal damage.	Stroke mouse model.	[5]

Table 1. *Cont.*

Condition	TNF-α family member	Tissue	Finding	Model	Ref.
Multiple sclerosis (MS)	TNF-α	CNS	TNF-α levels are increased in MS lesions.	Human MS brain tissue.	[140,141]
			Constitutive TNF-α overexpression can cause a spontaneous inflammatory demyelinating disorder.	TNF-overexpressing mouse model.	[142]
			TNF-α knockout increases demyelination and inflammation.	EAE mouse model.	[144,145]
			TNF-α knockout delays both demyelination and remyelination.	Cuprizone mouse model.	[146]
			General blockage of TNF-α by etanercept is linked to onset of MS in human case reports.	Human case reports.	[157,158]
			General blockage of TNF-α by lenercept may exacerbate symptoms in human MS patients.	Human MS patients.	[156]
	TNFR1	CNS	TNFR1 knockout mice do not develop EAE or have a less severe disease course.	EAE mouse model.	[18, 152–154]
			TNFR1 signaling induces oligodendrocyte apoptosis and primary demyelination.	TNF-transgenic mice.	[147]
			TNFR1 may contribute to inflammatory infiltration of the spinal cord.	EAE mouse model.	[148]
			Selective inhibition of TNFR1 signaling ameliorates EAE-induced pathology.	EAE mouse model.	[18,149]
			sTNF-α inhibition protects against EAE symptoms.	EAE mouse model.	[150,151]
	TNFR2	CNS	TNFR2 knockout mice show aggravated demyelination and disease symptoms.	EAE mouse model.	[18, 152–154]
			TNFR2 signaling mediates remyelination and oligodendrocyte precursor cell proliferation.	Cuprizone mouse model.	[146]
			Selective stimulation of TNFR2 protects primary oligodendrocytes from oxidative stress.	Primary oligodendrocyte cell culture.	[155]

3.5. Other Neurodegenerative Disorders

Besides the four conditions described above, there are certainly many other disorders with neurodegenerative features in which a role for TNF-α has become clear. Although for this review we have chosen to focus on AD, PD, ischemic stroke, and MS, investigation of TNF-α and its receptors in other neurodegenerative conditions may also greatly contribute to the understanding of TNF-α's effects, and the factors on which these effects depend. Examples of other disorders in which TNF-α has been implicated include traumatic brain injury (TBI) [167], epilepsy [168], and Huntington's disease (HD) [169,170]. Evidence exists that TNFR1 signaling may exacerbate cognitive dysfunction in a mouse model of TBI, while TNFR2 signaling may attenuate it [171,172]. Also, in models of epileptic seizures, inhibition of TNFR1 signaling as well as activation of TNFR2 were suggested to protect against seizure-induced neuronal damage [168,173,174]. In *in vitro* and *in vivo* models of HD, blockage of sTNF-α by XPro-1595 was shown to reduce different pathological features of HD [175]. Another group of diseases in which TNF-α signaling may play an important role is lysosomal storage disease (LSD). LSDs are rare, and result from mutations in lysosomal enzyme-encoding genes, causing the enzyme's substrate to accumulate in the lysosomes. Depending on the enzyme that is affected, different substrates may pile up, leading to different LSDs. More than 30 LSDs are known, and include, for example, Fabry disease, Pompe disease, Gaucher disease, and Niemann-Pick type C (NP-C) disease [176]. In the majority of LSDs neurodegeneration occurs, with neuroinflammatory processes being implicated as important contributors [177–179]. In human NP-C patient brain tissue as well as in a mouse model of this disease, apoptotic neurons were detected. Interestingly, in affected brain regions in an NP-C mouse model, the expression of different components in TNF-mediated apoptotic signaling was found to be increased, including that of TNF-α itself, TNFR1, and caspase-8 [180]. Gaucher disease patients showed elevated serum TNF-α levels, and in the fetal brains of a Gaucher disease mouse model, TNF-α levels (as well as the levels of different other pro-inflammatory cytokines) were increased [181,182]. Also, after birth, TNF-α and TNFR1 were found to be upregulated in the brains of Gaucher disease mice with increasing age and disease severity [183]. All in all, there are many conditions with neurodegenerative components in which TNF-α signaling may significantly contribute to neuropathological processes, and more research focusing on TNF-α signaling via either TNFR1 and TNFR2 is warranted.

4. TNFR1- and TNFR2-Mediated Signaling in Neurodegeneration

Despite the overlap between the signaling pathways of TNFR1 and TNFR2, their effects can differ greatly. For example, although both receptors may cause activation of transcription factor NF-κB (however with different activation kinetics [59]), different genes are transcribed depending on which TNFR was activated. The involvement of possible TNFR1 and TNFR2 downstream signaling pathways in neurodegenerative disorders will be discussed based on studies using TNFR1- and/or TNFR2-specific knockout animals, or compounds targeting TNFRs specifically.

4.1. TNFR1—Possible Downstream Targets in Neurodegeneration

Neutrophil gelatinase-associated lipocalin (NGAL, also known as lipocalin 2, the murine orthologue of NGAL) is a recently described downstream product of TNFR1-mediated signaling [184]. NGAL plays

a role in the innate immune system, and is important in the defense against certain bacteria [185]. Mounting evidence recently provided insights into interesting functions of NGAL in the brain, particularly its role in neurodegenerative disorders. Robust increased NGAL protein levels were found in AD post-mortem human brain tissue [184], a mouse model for MS [186], and mouse model for cerebral ischemia [187]. Increased NGAL protein levels are detrimental to neuronal health [188] and sensitize neurons and other brain cell types to cell death upon exposure to Aβ and oxidative stress [184,189,190]. In addition, NGAL was shown to further promote pro-inflammatory reactions, and to stimulate classical inflammatory activation of microglia and astrocytes [191,192]. NGAL plays an interesting role in TNF-α-mediated signaling pathways. Our research group showed that NGAL is solely increased and secreted upon TNFR1 stimulation in murine primary neurons, astrocytes, and microglia cells. Increased NGAL in turn silences the TNFR2-mediated PI3K-PKB/Akt pathway in neurons, possibly by increasing PTEN levels [184]. Thus, NGAL may play an important role in shifting TNF-α signaling towards TNFR1-mediated pathways observed in different neurodegenerative conditions, as previously described in this review.

Different studies demonstrated that TNFR1 can induce matrix metalloproteinase 9 (MMP-9) expression [193–195]. In the A549 cell line (a human lung adenocarcinoma epithelial cell line), TNF-α can induce MMP-9 expression via a TNFR1/TRAF2/PKC alpha-dependent pathway [193]. MMP-9 has been associated with different physiological and pathophysiological processes. For example, MMP-9 was shown to be able to interact with Aβ, and can play a role in the disruption of the blood-brain barrier [196–199]. This latter effect seems to be associated with MMP-9's actions in the degradation of the extracellular matrix. Of note, it was shown that MMP-9 can form a complex with NGAL, and that NGAL may elongate the activity of MMP-9 [200].

TNFR1 could engage in processes concerning the clustering of the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor (AMPAR). Deletion of TNFR1 was found to suppress excitatory synaptic transmission via the localization of AMPA receptors to the synapses of cortical neurons [201]. It was therefore suggested that TNFR1 might be involved in AMPAR-mediated excitotoxicity. Furthermore, it was shown that TNFR1 signaling induces excitotoxicity by promoting glutamate release in mouse primary microglia and astrocyte cell cultures [202–204]. More specific to AD, TNFR1 was found to be involved in the processing of the amyloid precursor protein (APP) and Aβ plaque formation by increasing BACE1 promotor activity [91].

4.2. TNFR2—Possible Downstream Targets in Neurodegeneration

Examples of TNFR2-specific signaling in neurodegeneration have also been described [16,59]. Dolga *et al.* identified certain small conductance calcium-activated potassium K(Ca)2 channels as downstream products of TNFR2 signaling [129,205]. These channels contribute to neuroprotection against neuronal overstimulation by lowering the neuronal excitability. It is specifically the expression of K(Ca)2.2 that was shown to be downstream of TNF-α/TNFR2 signaling via NF-κB activation. As such, it was suggested that in primary cortical neurons, TNF-α induces K(Ca)2.2 channel activation, resulting in neurons that are more resistant to excitotoxic cell death by preventing intracellular calcium levels to become pathologically high [129,205]. In the past years it has been shown that K(Ca)2 channels may

also be involved in mechanisms contributing to the plasticity of the hippocampal CA1 neurons and in learning and memory [206,207].

Fischer *et al.* (2014) showed that TNFR2-mediated activation of the PI3K-PKB/Akt pathway in primary astrocytes induces the expression of different neuroprotective genes, including the gene that encodes leukemia inhibitory factor (LIF) [208]. LIF is a neurotrophic cytokine, which, in the brain, is mainly produced by astrocytes. Elevated levels of LIF were shown to promote the maturation of oligodendrocytes [208], and LIF was found to protect primary neurons against excitotoxicity [209]. Moreover, in the EAE mouse model LIF was demonstrated to protect axons in the brain from acute inflammatory damage [210].

Other downstream products of TNFR2 signaling include CXCL12, which has also been implicated in the proliferation and differentiation of oligodendrocyte progenitor cells [211]. Moreover, its levels were found downregulated in the Tg2576 AD mouse model, and reduced CXCL12 levels were shown to cause impairments in learning and memory [212]. Lastly, TNFR2 signaling in microglia has been related with the induction of anti-inflammatory pathways, for example the upregulation of IL-10 [213].

All examples discussed in this chapter support the idea that TNFR1 may specifically induce factors that contribute to neurodegenerative processes, while TNFR2 specifically mediates factors involved in neuroprotective mechanisms (Figure 3). However, in agreement with the rest of this review, things are certainly far more complex. Therefore, different unknowns and contradictory findings underlining and adding to the complexity of TNF signaling will be addressed in the following chapter.

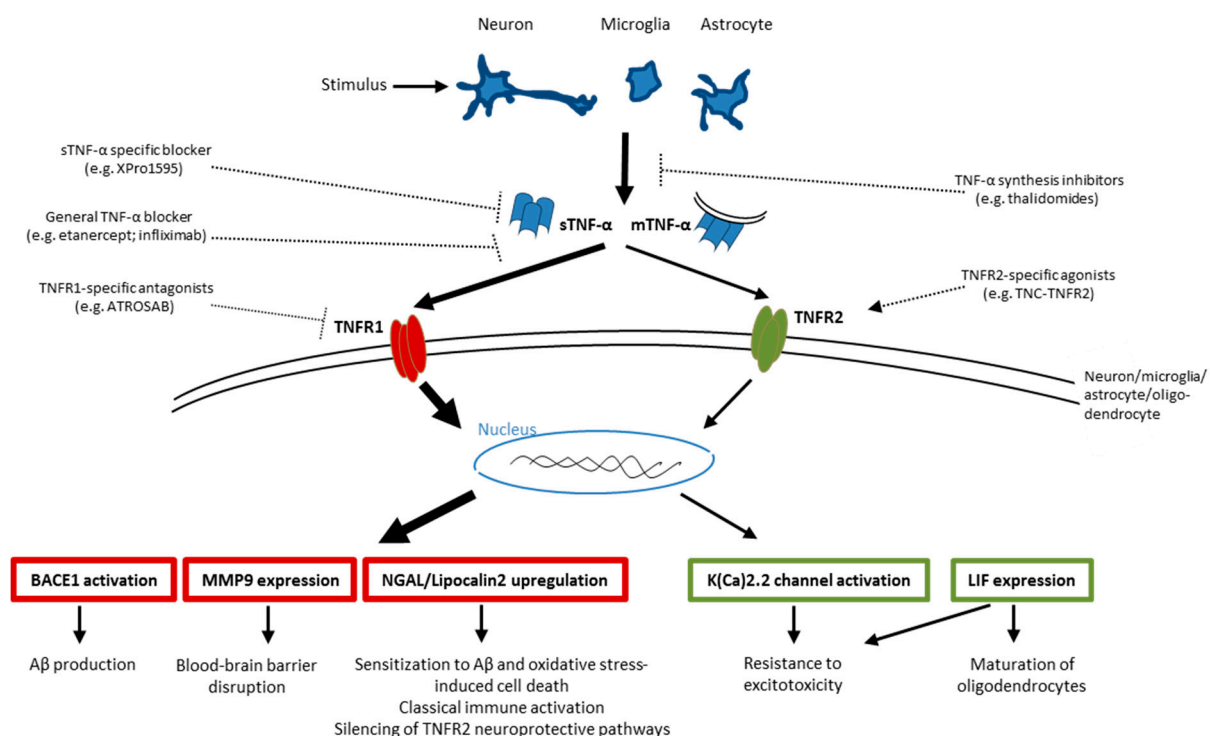**Figure 3.** Examples of specific downstream targets of TNFR1 and TNFR2 that may be involved in neurodegenerative disorders. Dotted lines indicate existing potential therapeutic approaches. Other general TNF-α blockers, not depicted in this figure, include adalimumab, certolizumab pegol, and golimumab. Other new TNFR1-specific antagonists include DMS5540 and TROS (also see review by Fischer *et al.*, 2015 [214]).

5. Complex matters: TNFR1 Signaling Is Primarily Damaging and TNFR2 Beneficial?

Although in this paper we generally highlighted an important neuroprotective role for TNFR2 and a neurodegenerative role for TNFR1 in different neurodegenerative disorders, findings that contradict this idea cannot be ignored. As described in the previous paragraphs, for several neurodegenerative disorders conflicting results have been found concerning beneficial/detrimental effects of TNFR1 and TNFR2 signaling. These contradictory findings emphasize the complexity of TNFR1/TNFR2 signaling, and confirm that our understanding of TNF signaling is still a work in progress.

The outcome of TNF-α signaling will likely depend on many variables: the availability of both receptors, the available levels of sTNF-α and mTNF-α ligands, the availability of the components in their respective signaling cascades, and the level of crosstalk between the two pathways, all of which likely depend on the cell type, tissue, and the condition. Indeed, different studies have suggested that TNF-α signaling may be strongly brain region-specific, which may in part depend on, e.g., the relative density and activity of microglia in specific regions [213,215,216]. Also, the timing of TNF-α signaling in different stages of neurodegeneration could affect the outcomes of TNF-α. For example, TNF-α mediates a neuroprotective effect when hippocampal organotypic slice cultures are treated with TNF-α before an ischemic insult (which may simulate ischemic preconditioning), but has neurotoxic effects when administered after the same ischemic insult [217]. Furthermore, TNFR2-mediated pathways have received less attention compared to TNFR1, and undefined signaling mechanisms possibly remain to be discovered. These and other factors greatly increase the complexity of TNF signaling, and a few will be further discussed below.

5.1. Selective Harmful Downstream Targets of TNFR1 and Beneficial Downstream Targets of TNFR2?

Although Chapter 4 described examples supporting the presence of potent detrimental downstream signaling pathways mediated specifically via TNFR1, while TNFR2 signaling may mostly activate genes with potential neuroprotective functions, matters are often not that clear-cut. For instance, it should be noted that there are certain examples available of neuroprotective pathways induced via TNFR1, and damaging outcomes of TNFR2 signaling. For example, a known downstream target of TNFR1 is nerve growth factor (NGF), which is important for the survival and growth of neurons [218], while TNFR2 may also promote expression of potentially detrimental factors, such as intercellular adhesion molecule-1 (ICAM-1), which has been associated with neuroinflammation and neurodegeneration [219,220]. Moreover, the specificity of certain downstream products to either TNFR1 or TNFR2 is sometimes unclear. For example, some studies have implied NGF to be solely induced via TNFR1 in fibroblasts, while it appeared in astrocytes that signaling via both receptors can cause NGF production [218,221]. Such contradictory findings may, among others, depend on variables like the cell type studied, the proximate cellular conditions, TNFR1-TNFR2 signaling kinetics, and crosstalk between the receptors. In addition, although the above-described processes were found to be specifically induced via either TNFR1 or TNFR2, there may very well be multiple other (TNF-α-independent) pathways that may influence TNF-α-mediated pathways and their outcomes. For example, it may be good to keep in mind that lymphotoxin α (TNF-β) can also bind both TNFR1 and TNFR2. Comparable to TNF-α, lymphotoxin α also has been implicated in different processes in the brain, and in the pathogenesis of conditions including MS [222,223].

5.2. Soluble TNF Receptors

Adding to the complexity of TNF-α signaling, besides membrane TNF receptors (mTNFRs), soluble TNF receptors (sTNFRs) also exist, which influence TNF-α signaling mechanisms as well. sTNFRs (sTNFR1 and sTNFR2) can be formed via a process known as ectodomain shedding, in which the extracellular domains of membrane TNFRs are cleaved off by TACE (which thus shows to have more targets besides mTNF-α) and released into the extracellular space. Notably, in addition to ectodomain shedding, it has been described that TNFR1 can also end up in the extracellular space via exocytosis. This generates exosome-like vesicles with full-length TNFR1 incorporated in the vesicle membrane [224]. The exact functions and mechanisms of actions of sTNFRs (as well as the full-length TNFR1 within vesicles), however, remain elusive. Shedding of mTNFRs is thought to regulate the actions of TNF-α, firstly by diminishing the number of mTNFRs on the cell membrane, and secondly by binding of sTNFRs to TNF-α, thereby preventing TNF-α from binding to and activating mTNFRs. Alternatively, it was suggested that sTNFRs bind to sTNF-α and subsequently stabilize and preserve the bio-active trimeric forms of TNF-α [225]. As such, sTNFRs levels might reflect the activity of TNF-α. Interestingly, intravenous injection of TNF-α in human volunteers suggested that TNF-α is a potent mediator of increased sTNFR1 and sTNFR2 release [226].

Different studies indicate that the levels of sTNFR1 as well as TACE activity are increased in plasma, serum, and CSF from AD patients [159–163]. Moreover, Diniz *et al.* (2010) showed that higher serum sTNFR1 levels can predict conversion from mild cognitive impairment (MCI) to AD [161]. Plasma and CSF sTNFR2 levels were found to be increased in AD by some groups [159,160], while other studies showed no differences in sTNFR2 levels [161,162]. Similar to AD, increased serum sTNFR1 levels were found in patients with PD [102,104,165]. Also, a single nucleotide polymorphism in the gene encoding TNFR1, resulting in production of a soluble form of TNFR1 that is able to antagonize TNF-α, was found to be associated with MS [227]. Although in these cases the exact meaning of these increased serum sTNFR1 levels is not clear, it was found that higher serum sTNFR1 levels are associated with a later onset of sporadic PD [165]. In addition to the potential functions and effects of sTNFRs described above, sTNFRs may also influence TNF-α signaling via reverse signaling through mTNF-α.

Besides being a ligand for TNFR1 and TNFR2, mTNF-α can also act as a receptor itself. Thus, in addition to inducing a signaling cascade in TNFR1/TNFR2-expressing cells, mTNF-α can also elicit a signal transduction pathway back into the cell on which it is expressed [228]. This process is called reverse signaling, and can occur when mTNF-α is bound by a (s)TNFR or agonistic antibody [228,229]. sTNFRs may have significant effects on cells by inducing reverse signaling. For example, it was reported that sTNFR1 can induce apoptosis of monocytes through reverse signaling via mTNF-α. It appeared that this sTNFR1-induced apoptosis is independent of death receptor pathways, but is mediated via autocrine transforming growth factor beta (TGF-β) through p38 MAPK [230]. In addition, it was recently shown in cultured superior cervical ganglion (SCG) neurons that sTNFR1 promotes sympathetic axon growth and branching through reverse signaling via mTNF-α, and relies on downstream activation of ERK [231].

In addition to endogenous (s)TNFRs, different TNF-α inhibitors (such as etanercept and infliximab) can induce reverse signaling through mTNF-α as well. As suggested in recent studies, effects of such compounds may significantly depend on reverse signaling, besides the effects arising from the prevention of mTNF-α and sTNF-α to bind their TNFRs [232,233].

Taken together, soluble TNFRs may play a substantial role in how TNF-α interacts and functions with its receptors, possibly especially in a systemic pro-inflammatory environment. This is an interesting and noteworthy research field that can provide important insights in TNF-α functioning. In theory, a potential therapeutic strategy to reduce excessive TNFR1 signaling may be to stimulate TNFR1 ectodomain shedding. Interestingly, some mediators (with aminopeptidase regulator of TNFR1 shedding (ARTS-1) appearing as a key regulator) have been identified that are essential for TNFR1 shedding but do not affect TNFR2 shedding [234,235]. While ARTS-1 also participates in shedding of other receptors besides TNFR1 (including IL-6R and IL-1R2 [236]), downstream effectors of ARTS-1 may prove to be TNFR1-specific, and could provide a therapeutic target.

5.3. Interaction between TNFR2 and Interleukin-17 Receptor D

Moreover, the signaling of membrane TNFRs may also hold more complexity than has become clear so far. For example, it was very recently demonstrated that TNFR2 (but not TNFR1) can form a heteromer with interleukin-17 receptor D (IL-17RD, also known as Sef), leading to activation of NF-κB signaling via TRAF2 recruitment [237]. Depletion of IL-17RD was found to impair TNFR2-mediated activation of NF-κB. The complex between IL-17RD and TNFR2 was shown to be formed in HK-2 and 786-O cell lines (a human proximal tubular cell line derived from normal kidney and a human renal cell adenocarcinoma cell line, respectively), and also in rat and mouse renal tissue. This indicates that the interaction between TNFR2 and IL-17RD may arise under physiological conditions [237].

All these complex issues and unknowns emphasize that gaps remain in the basic understanding of TNF-α signaling, which may challenge the identification of suitable TNF-targeting therapeutics for different neurodegenerative disorders.

6. Targeting TNF-α Signaling: An Opportunity for Treatment of Neurodegenerative Disorders?

As concluded in this review, targeting TNF-α signaling towards its neuroprotective functioning could provide potent therapeutic strategies for patients with neurodegenerative disorders. It seems that therapeutics could aim at a certain step of TNF-α-mediated signaling pathways via inhibiting detrimental pathways.

6.1. Targeting TNF-α as Treatment for Neurodegenerative Disorders

Because TNF-α is a key inductor in some inflammatory diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), Crohn's disease (CD), as well as some neurodegenerative disorders, directly inhibiting this cytokine could prevent or treat those conditions. A number of researchers have demonstrated that directly blocking the actions of TNF-α via anti-TNF-α antibodies and its antagonists indeed can ameliorate inflammatory and neurodegenerative disorders [238–240]. Additionally, inhibition of sTNF-α was shown to promote axon preservation and remyelination in the EAE mouse model [151]. Due to its therapeutic capability, treatments aimed at inhibiting the functions of TNF-α have been shown as effective treatment strategies for RA, PsA, and CD in experimental trials and are currently being used worldwide in the clinical setting [19,241–243]. So far, pharmaceutical anti-TNF-α agents that include thalidomide analogues which inhibit the production of TNF-α have been applied for the treatment of RA [244–246]. Moreover, other pharmaceutical agents including etanercept, adalimumab,

and infliximab, which can bind both sTNF-α and mTNF-α, thereby inhibiting their signaling, have been successfully applied for treatment for RA and PsA [247]. Studies into the effects of such pharmaceuticals in neurodegenerative disorders like AD, PD, and MS, however, remain limited.

Drugs targeting TNF-α for systemic inflammatory diseases still have adverse effects in a minority of patients [248]. For instance, anti-TNF-α therapy for RA induces the risk of serious infections of the skin, soft tissues, and joints [249]. Anti-TNF-α agents increase risk rates of malignancies in patients with inflammatory bowel disease [250]. It has been mentioned that two patients with rheumatoid arthritis treated with an anti-TNF-α strategy developed neurological symptoms, including demyelination lesions [251]. Furthermore, it was shown that newborns presented severe neutropenia after their mothers were treated with infliximab for ulcerative colitis during pregnancy [252].

To reduce or diminish the drawbacks of anti-TNF-α agents in inflammatory diseases and neurodegenerative disorders, other therapeutic strategies should be investigated. Considering the various outcomes of TNF-α, targeting a specific point in its signaling pathways could be more effective and decrease the negative effects associated with anti-TNF-α agents.

6.2. Targeting TNFRs as Treatment for Neurodegenerative Disorders

In essence, TNFR1 has often been demonstrated to deteriorate or aggravate neurodegeneration, whereas TNFR2 mediates neuroprotection. Therapeutics that specifically modulate the signaling mechanisms of TNF-α, *i.e.*, blocking TNFR1 actions and/or increasing the TNFR2 signaling pathway, could greatly reduce the side effects of current anti-TNF-α approaches. Sedger's group [253] discovered that a leporipoxvirus TNF receptor homolog by its N-terminal preligand assembly domain (PLAD)-homologous domain interacts with the intracellular domain of TNFR1 and showed that this interaction results in a heterocomplex that inhibits TNFR1 downstream signaling and significantly prevents TNFR1-induced apoptosis of lymphocytes. Selectively blocking the bioactivity of sTNF-α, thus preventing TNFR1-mediated signaling, attenuated the pathological symptoms in EAE mice [150,151]. Furthermore, a soluble TNFR1-selective antagonistic mutant TNF (named R1antTNF) ameliorated the symptoms in EAE mice [149,254]. Currently, an antagonistic TNFR1-specific antibody has been produced and demonstrated to treat MS clinical symptoms more efficiently in EAE mouse model [18]. Another human TNFR1-specific antagonistic antibody that may prove to have therapeutic effects is ATROSAB [255,256].

As TNFR1 is mainly activated by sTNF-α, selectively inhibiting sTNF-α may prevent TNFR1-mediated apoptosis and could be a therapeutic strategy in neurodegenerative disorders. In this regard, a blocker of sTNF-α, XPro-1595, significantly improved the cognitive deficits induced by spinal cord injury in mice compared to the drug etanercept [257]. Furthermore, Tansey *et al.* [258] discovered that XPro-1595 significantly reduced activation of microglia and astrocytes, and prevented loss of dopamine neurons in a rat model of PD. Shedding of TNFR1 mediated by iNOS-cGMP-TACE signaling has been suggested to significantly ameliorate the inflammation associated with sepsis [259]. Increased sTNFR1 levels resulting from this TNFR1 shedding could compete to bind to sTNF-α and impair TNFR1-mediated downstream signaling pathways and potentially reduce its apoptotic signaling pathways.

TNFR2-mediated signaling could be used as a therapeutic approach for neurodegenerative disorders. Lovastatin, which is widely used to reduce cholesterol levels in patients, has been confirmed to selectively increase TNFR2 expression [260]. Thereafter, it was demonstrated that lovastatin protected

primary cortical neurons against glutamate-induced excitotoxicity [261]. Moreover, *in vivo* evidence showed that lovastatin attenuated NMDA-induced nucleus basalis magnocelullaris (NBM) lesions and prevented cognitive deficits in mice [262]. This further supports the idea that TNFR2 activation could be a therapeutic approach for neurodegenerative disorders. Notably, Pfizenmaier's group [110] constructed a soluble human TNFR2-selective agonist (TNC-scTNF$_{R2}$) and demonstrated that it successfully rescues human neurons from oxidative stress-induced cell death. TNC-scTNF$_{R2}$ is synthesized by genetic fusion of the trimerization domain of tenascin C to a TNFR2-selective single-chain TNF molecule, which specifically activates TNFR2 to promote the PI3K-PKB/Akt-NF-κB signaling pathway and promotes neuroprotection.

Selective targeting of TNFRs as a therapeutic strategy seems a promising avenue for the treatment of CNS conditions and some inflammatory diseases associated with TNF-α. Of note, it should be established whether simultaneous targeting of both receptors is necessary to achieve maximum therapeutic efficacy, as compared to inhibition/stimulation of either TNFR1 or TNFR2. Moreover, the ability of therapeutic compounds to cross the blood-brain barrier (BBB) is an obstacle that needs urgent attention. TNF-α blockers like etanercept and infliximab are too large to penetrate the BBB and, of certain new compounds, it is yet to be examined whether they can pass the BBB. In the EAE mouse model, subcutaneous or intraperitoneal injections with XPro-1595 and R1antTNF were effective in reducing pathology [149–151]. However, seeing the involvement of the peripheral immune system in MS and EAE, it may be that targeting peripheral TNF-α is sufficient to reach therapeutic effects. Moreover, since the BBB is compromised in the EAE model, a possibility exists that these compounds may have entered the brain through an already leaky BBB. Nevertheless, a recent study on XPro-1595 in the 6-OHDA model for PD (in which the BBB is presumably not damaged enough to let XPro-1595 pass non-selectively) revealed that this compound could indeed reach the brain in therapeutically relevant concentrations (evidenced by inhibited glial activation and reduced dopamine neuron loss), after subcutaneous administration [258]. Moreover, it may be that certain compounds, in certain conditions, do not necessarily have to pass the BBB to reach therapeutic effects. For example, in rat MCAO models for cerebral ischemia beneficial effects were reported upon intraperitoneal injection of etanercept [124,125]. However, it may be that etanercept could enter the brain via disruptions in the BBB, induced by the MCAO [124]. Other important issues that will need to be addressed include the timing of treatment, and the potential side-effects that may arise from targeting TNF-α, TNFR1, and/or TNFR2. In case of ischemic stroke, start the treatment within a few hours upon an insult may be crucial to limit damage as much as possible. As described in Chapter 3.3, the timing of specific TNF treatments may be particularly delicate in acute conditions where TNFR expression levels may be rather dynamic in the first hours/days, for example after the stroke. Apoptotic signaling may be beneficial immediately upon an insult in order to clear damaged cells and protect surrounding cells. As such, administering, e.g., TNFR1 antagonists, may have to be very carefully timed, neither too early nor too late. However, for chronic conditions such as AD, PD, and MS, it can be hypothesized that beginning treatment in early stages may in the end prove to be most effective, but starting treatment in later stages may well slow down the neurodegenerative process. Furthermore, potential side-effects of TNF-targeting compounds have to be assessed. For example, the possibility that selective inhibition of TNFR1 or stimulation of TNFR2 signaling could negatively affect production or action of neurotrophic factors (such as NGF and BDNF) should be explored in future studies.

7. Conclusions

As discussed in this review, TNF-α is involved in many neurodegenerative disorders by exerting both neuroprotective and neurodegenerative functions. A balance between these opposite effects seems to depend on its actions via TNFR1 and TNFR2. A thorough understanding of TNF-α signaling pathways can contribute to the development of potential therapeutic strategies. Focusing on multiple molecular interactions, which can control signaling outcomes in TNF-α signaling pathways, could be critical to develop preferable therapeutic strategies in the future.

Acknowledgments

Author Contributions

Yun Dong and Doortje W. Dekens wrote the manuscript and designed the figures. Peter Paul De Deyn, Petrus J.W. Naudé and Ulrich L. M. Eisel reviewed and revised the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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