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Tumor Necrosis Factor-alpha Mediated Signaling in Neuronal Homeostasis and Dysfunction

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Abstract

Tumor necrosis factor-alpha (TNF-α) is a potent pro-inflammatory molecule, which upon engagement with its cognate receptors on target cells, triggers downstream signaling cascades that control a number of cellular processes related to cell viability, gene expression, ion homeostasis, and synaptic integrity. In the central nervous system (CNS), TNF-α is produced by brain-resident astrocytes, microglia, and neurons in response to numerous intrinsic and extrinsic stimuli. This review will summarize the key events that lead to TNF-α elaboration in the CNS, and the effects that these inflammatory signals impart on neuronal signaling in the context of homeostasis and neuropathology.

Keywords

TNF-α; neuroinflammation; Alzheimer's; Parkinson's; synaptic plasticity; ionic homeostasis

1. Introduction

Inflammatory signals incited within the central nervous system (CNS) and peripheral tissues regulate diverse biological processes. Inflammatory molecules, which are generated by surveilling immune cells and/or organ-resident cells, can arise in response to tissue damage, cellular dysfunction, and infection, and work via activating intracellular signaling cascades that eventually lead to immune cell activation, proliferation, cell recruitment, or cellular demise. A self-limiting inflammatory response can result in resolution of the insult through removal of damaged tissue or neurotoxic proteins to return the CNS to its normative state. However, if the immune response persists, a state of chronic neuroinflammation can develop. Unchecked neuroinflammatory activity may over time lead to cellular dysfunction and diminished viability. Several debilitating neurodegenerative diseases harbor coincident

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chronic neuroinflammation [1–4], indicating an absence of tight regulation over CNS-resident inflammatory responses may underlie disease pathogenesis.

Of particular importance in the genesis of inflammatory events are the immunomodulators referred to as cytokines [5]. Although each of these factors plays varying roles in driving inflammatory responses, tumor necrosis factor-alpha (TNF-α) has been demonstrated to act as a central mediator with broadly ranging activities. From its initial description in peripheral inflammatory responses, this cytokine is unique in its ability to induce selective necrosis of cancerous cells, while simultaneously sparing normal counterparts. These seemingly contradicting functions are now becoming more clearly defined in neuroinflammatory events arising within the developing and adult CNS. This review will focus on the pathways by which TNF-α modulates homeostatic and pathogenic neuronal signaling within the CNS compartment.

2.1 Tumor necrosis factor-alpha

TNF-α was first described by Carswell and colleagues in 1975 as a proteinaceous component of serum from bacterially challenged mice, and was shown to induce the death of cancer cell lines *in vitro* and eliminate transplanted sarcomas *in vivo* [6]. Interestingly, this molecule was able to elicit this death response without deleteriously affecting normal cell viability. Subsequent molecular isolation and characterization of the TNF-α gene indicated that this cytokine is a 212-amino acid protein that localizes to the cell surface in a pro-form [7]. This type-II transmembrane protein is active in cell-associated and soluble forms, the latter of which is released following proteolytic cleavage by TNF-α cleaving enzyme (TACE) [8].

TNF-α is produced in response to a variety of CNS insults. Exogenous signals, such as those arising from exposure to bacterial and viral proteins, potently induce inflammatory responses within the CNS [9,10]. Infusions of lipopolysaccharide (LPS), a component of Gram-negative bacterial cell walls, have been used to experimentally mimic bacterial infections within the brain. Introduction of this molecule in the CNS activates toll-like receptors (TLR) on glial cells and induces the activation of microglia [11]. Through this activation process, LPS stimulates the expression of a multitude of cytokines, including interleukin (IL)-1, 6, and 12, cyclooxygenase-2 (COX-2), and TNF-α [12,13]. Human immunodeficiency viral (HIV) infection of peripheral immune cells can eventually lead to infiltration into the CNS, inducing the expression of several pro-inflammatory cytokines, including TNF-α [14]. Furthermore, non-productive infection with Herpes Simplex Virus (HSV) can also lead to chronic microglial activation and the subsequent elaboration of TNF-α [9].

In addition to exogenous signals, TNF-α expression is also induced by cell-intrinsic stimuli relating to physical damage. Neuronal lysates added to Schwann cells of the peripheral nervous system induce expression of MCP-1, iNOS, and TNF-α [15,16]. Further investigation determined that this effect was mediated by type-2 and 3 Toll-like receptors, suggesting that neuronally harbored factors can activate inflammatory responses [15]. Similar observations have been made in the CNS where transection of neuronal axons in the entorhinal cortex of the brain leads to the up-regulation of Toll-like receptors on proximal microglial cells ultimately resulting in enhancement of chemokine and cytokine expression, release of reactive oxygen species and further microglial recruitment [17]. Mammalian nucleic acids can stimulate the generation of TNF-α and other inflammatory mediators [18]. Antibodies specific to self-RNA and DNA oligonucleotides can activate TLR-7 and 9, which results in the production of pro-inflammatory cytokines. Furthermore, the abnormal release and/or uptake of neurotransmitters, such as glutamate, can result in the activation of CNS inflammation [19]. Naïve neuron/astrocyte co-cultures exposed to oxygen-glucose

deprivation, a model of the ischemic conditions associated with stroke, led to the activation of resident microglia. This activation was attributed to the increased presence of glutamate in the co-cultures, which led to metabotropic glutamate receptor activation on the surface of microglia cells and coincident TNF-α expression [19]. These studies, in aggregate, serve to illustrate that a variety of insults result in the generation of TNF-α. For a biologically relevant response to arise, this cytokine must be detected by a given target cell, leading to the transduction of disparate intracellular signaling cascades that ultimately impact cellular physiology.

2.2 Tumor necrosis factor-alpha signaling

TNF-α interacts with two cognate receptors: p55 (TNF-RI) and p75 (TNF-RII) (Figure 1). These receptors are expressed on neurons, astrocytes, and microglia throughout the CNS [20]. Binding of homotrimeric TNF-α to either receptor can activate three major signaling cascades [21]. First, an apoptotic signaling cascade is initiated when the ligand-bound TNF receptor associates with the TNF receptor-associated death domain (TRADD) domain. This results in recruitment of Fas, internalization, and subsequent activation of caspase-8 [22]. However, it is not entirely certain that this cascade always results in apoptosis, since a subset of studies have indicated that TNF-α rarely induces apoptosis in the absence of a secondary signal [23]. The second major cascade that can be activated by TNF-α is the nuclear factor kappa B (NFκB) signaling pathway. NFκB signaling is initiated when phosphorylation of its inhibitory subunit (IκB) via NEMO (NFκB essential modulator) occurs, which leads to the dissociation and eventual degradation of IκB (reviewed in [24]). NFκB, a dimerized protein consisting of Class I (p50) and II (Rel) subunits, subsequently translocates to the nucleus where it regulates gene transcription by binding to specific DNA sequences, and depending on binding sequence composition, acts as either a transcriptional activator or repressor [24]. In contrast to the activation of the TRADD domain, the activation of NFκB signaling by TNF receptor stimulation is hypothesized to promote pro-survival signal cascades [25], indicating again the dichotomistic ability of TNF-α to induce both pro-life and pro-death cellular outcomes. The third major signaling cascade activated by TNF-α engagement with its cognate receptors is the JNK (c-Jun N-terminal kinase) pathway. Activation of this pathway can result in the enhanced activity of several transcription factors, including activator protein-1 (AP-1) and specificity protein-1 (SP-1), via JNK-mediated phosphorylation [26]. These transcription factors can then go on to either positively or negatively regulate gene expression based on co-factor expression profiles and binding site composition within promoter regions of target genes. JNK can also promote both cell survival by regulating c-Jun and cell death via regulating c-myc and p53 activity [27–30]. Ultimately, the activity of any or all of these downstream pathways is believed to depend upon the cell type-specific expression of TNF receptor coupling proteins and points of crosstalk between the NFκB and JNK pathways [31–33].

Through this diverse signaling network, TNF-α regulates numerous physiologically important processes in the CNS, including neuronal development, cell survival, synaptic transmission, and neuronal ionic homeostasis [21,22,34,35]. In the next several sections, the ability of TNF-α to modulate these processes will be further detailed.

2.3 TNF-α and neuronal development

The genetic ablation of the TNF-α gene has been observed, surprisingly, to not result in gross deficits in murine development [36]. However, studies finely examining the CNS-centric effects of pro-TNF-α deletion have shown interesting effects on neuronal maturation and arborization. Golan and colleagues examined the role of TNF-α in the development of the hippocampus [36]. They found that the lack of TNF-α expression resulted in accelerated dentate gyrus development, which they correlated to enhanced levels of nerve growth factor

(NGF). In contrast, they found that the dendritic arborization complexity of pyramidal neurons residing within the CA1 and CA3 regions of the hippocampus was reduced in the absence of cytokine expression. The examination of this effect *in vitro* through use of neuron/astrocyte co-cultures, however, indicated that treatment with TNF-α led to less dendritic branching, a deficit that could be rescued with genetic ablation of the neuronal TNF-R gene or with the addition of a soluble TNF-R construct [37]. Inverse experiments in which TNF-α was overexpressed in the CNS of transgenic mice by the insertion of a human β-globin promoter-driven TNF-α transgene have also been performed [38]. In agreement with the results from the genetic ablation study, TNF-α overexpression antagonized NGF production in the hippocampus and, possibly through this mechanism of diminished neurotrophin levels, thereby suppressing hippocampal development [39].

The behavioral effects of manipulating TNF-α expression have been further supportive of the immunohistochemical observations [39]. TNF-α-deficient mice exhibit a decreased latency in finding the underwater platform in the Morris water maze testing paradigm as compared to wild-type mice, suggesting enhanced hippocampal memory function in TNF-α knock-out mice [36]. Moreover, overexpression of TNF-α impaired hippocampal learning/memory function in Morris water maze assessments [39], indicating a suppressive role for high-level TNF-α in cognition.

Despite addressing the anatomical changes in hippocampal development and behavioral impact of these alterations that occur through the modulation of TNF-α expression, these prior studies have not fully addressed developmental effects of the pro-inflammatory cytokine in other areas of the CNS. The creation of more intricate transgenic models that allow for stage-specific enhancement and/or ablation of TNF-α signaling may elucidate additional functions of the cytokine in brain maturation.

2.4 TNF-α and neuronal viability

The induction of neuronal apoptosis can be mediated by a myriad of pathways. The TNF receptor superfamily consists of greater than 15 members and the binding of trimeric TNF-α to the majority of these receptor subtypes has the ability to initiate apoptosis [40]. This is made possible by the presence of a “death domain” sequence elucidated in TNF-RI [41]. This intracellular domain is approximately 80 amino acids long [41] with significant homology to the Fas antigen, a known inducer of apoptosis [42]. Additionally, this intracellular domain is relatively conserved within the TNF-R superfamily and its presence facilitates interactions between the receptor and several other binding partners, including TRADD and Fas-associated death domain (FADD) [43]. TRADD binds to the TNF receptor death domain via a homologous sequence at its C-terminus [44], while FADD can bind through its death domain to either the TNF-R or to TRADD [45]. The binding of these proteins facilitates the recruitment of pro-caspase-8 to a secondary domain on FADD, referred to as the “death effector domain” [46]. This process results in the oligomerization of pro-caspase-8 and its auto-cleavage into activated caspase-8. Subsequently, additional pro-caspases are activated by caspase-8, resulting in a cascade that can eventually lead to apoptosis [47]. Although this represents the primary TRADD-driven cascade, TRADD has also been shown to facilitate the binding and activation of other molecules, such as JNK and NFκB, which have been associated with pro-survival signaling cascades, further indicating TNF-α signaling is a complicated, multi-factorial process.

While some laboratories have reported direct TNF-α-mediated neuronal toxicity [48], many groups have demonstrated that TNF-α alone fails to activate apoptosis in the absence of a secondary signal, and can actually prevent apoptosis following exposure to several cellular insults [47,49,50]. It is therefore plausible that an appropriate cellular environment or secondary signal is necessary for the induction of neuronal death. For example, when the

glutamatergic analog kainite and TNF-α were injected directly into the spinal cord of mice, increased neuronal toxicity was observed [51]. Moreover, it is likely that the degenerating environments associated with chronic disease such as Alzheimer's and Parkinson's diseases are sensitized to inflammation-driven cell death through the presence of coincident oxidative stress [52–55].

The signaling cascade-dependent protective effect of TNF-α signaling on neuronal viability has been experimentally documented. When mice devoid of TNF-α receptor expression were subjected to cerebral ischemia an increase in neuronal death was observed. This outcome was attributed to an elevation in reactive oxygen species, suggesting TNF-α may induce a protective antioxidant response in response to ischemic events [56]. Similarly, in a glutamate model of neuronal excitotoxicity, stimulation of TNF-RII with TNF-α led to protection against neurotransmitter toxicity [25]. Lastly, cultures of hippocampal neurons were shown to be resistant to amyloid-beta induced toxicity when pretreated with TNF-α [50]. In aggregate, these data suggest that TNF-α may impact neuronal viability differently depending on receptor subtype engagement and upon the presence or absence of secondary signals arising from situational exogenous or endogenous stimuli.

2.5 TNF-α and synaptic plasticity

Electrophysiological experiments have elucidated several negative effects of TNF-α signaling on neuronal function. Experiments performed on hippocampal slices show that the addition of the pro-inflammatory cytokine decreases long-term potentiation (LTP), a electophysiological correlate of learning and memory [57]. This effect is also observed in the dentate gyrus, suggesting a broad antagonistic effect of TNF-α on LTP [34]. The mechanism of the effect is still under study, but it has been suggested that activation of p38 plays a central role in the reduction of early phase LTP in response to TNF-α, whereas protein expression alterations likely underlie late-phase deficits [35]. TNF-α signaling has also been shown to exact effects on long-term depression (LTD), another electrophysiological process purported to provide insight into memory consolidation. Mice deficient for TNF-α receptor expression display no LTD in response to Schaffer collateral stimulation. This outcome was attributed to a compromise in NFκB activation, suggesting TNF-α signaling is necessary for the development of LTD [58]. Importantly, these studies both suggest that the cytokine is intimately related to memory formation, since its presence can dramatically alter the strength of the synapse, and indicate the need for further experimentation on the link between pro-inflammatory signaling and cognition.

2.6 TNF-α and ionic homeostasis

In addition to modulating neuronal signaling at the circuit level, TNF-α can also modulate proteins associated with ionic signaling (Figure 2). The influence of this cytokine on ionic homeostasis is multifaceted, since the inflammatory cytokine has been shown to influence plasma membrane and intracellular ion channels, both via regulation of their membrane insertion and steady-state expression level. For example, TNF-α mediated activation of TNF-RI enhances tetrodotoxin-insensitive Na^+ channel currents at the plasma membrane in dorsal root ganglia (DRG) neurons [59]. These channels, named transient receptor potential vanilloid-1 (TRPV), may play a role in the process of TNF-α induced hypersensitization to heat stimuli. Furthermore, this p38-dependent enhancement in Na^+ channel activity suggests a depolarizing effect of the cytokine, possibly allowing the DRG neuron to achieve an increased firing rate. In stark contrast, experiments utilizing cortical neurons demonstrated that TNF-α signaling enhances outward K^+ current, indicating the cytokine may act to hyperpolarize the membrane potential of specific neuronal subtypes and subsequently lower their firing rates [60]. These latter experiments further demonstrated that the enhanced K^+

current helped cortical neurons avoid N-methyl-D-aspartate (NMDA)-induced excitotoxicity.

TNF-α can modulate the expression of ion channels, thereby altering the responsivity of neurons to neurotransmitters. The most prominent of these changes is the alteration of plasma membrane α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) channel expression [61–63]. *In vitro* experiments performed with soluble receptor antagonists to TNF-α have determined homeostatic levels of GluR1 are regulated by endogenous cytokine signaling [63]. Others have shown that upon TNF-R engagement, surface membrane expression of GluR1-containing AMPA receptors is enhanced [61–63], indicating these channels likely reside in proximally localized vesicles that when TNF-α is encountered, rapidly insert into the membrane via vesicular fusion [62]. These studies further demonstrated that the increase in AMPA receptor expression is specific to the GluR2-lacking AMPA receptor subtype [63], a significant finding since this receptor subtype is unique in facilitating Ca^{2+} entry. AMPA receptor expression enhancement was also shown to impart effects on mean excitatory post-synaptic currents (mEPSCs), indicating the mechanism could significantly influence hippocampal neurotransmission.

The data derived from studies of TNF-α-mediated effects on NMDA receptor currents have been more controversial. Groups have reported that TNF-α exposure leads to the down regulation of NMDA currents [64], while others have observed an opposite effect [65] or even no substantial change in NMDA receptor localization following neuronal exposure to the cytokine [61]. Sorting through these contradictory data sets is important since these extracellular ion channels may modulate cytoplasmic Ca^{2+} levels and play a role in the synaptic signaling alterations discussed above.

The chloride-permeable gamma-aminobutyric acid (GABA) receptor and voltage-dependent Ca2+ channels (VGCC) are also altered by TNF-α exposure. Experimentswith hippocampal neuronal cultures have indicated that TNF-α stimulation results in adown regulation of $GABA_A$ expression [63]. Additionally, it was demonstrated that this process occurs due to a significant enhancement in GABA receptor endocytosis and results in the reduction of mean inhibitor post-synaptic currents (mIPSCs). Although reports on this phenomenon are sparse, the authors strongly argue that a TNF-α driven down regulation of the inhibitory signaling (GABA) and enhancement in excitatory signaling (AMPA) may ultimately produce significant alterations in hippocampal signaling. Experiments performed on hippocampal neurons indicated prolonged exposure to TNF-α enhances L-type Ca^{2+} channel conductance by approximately 45%, with N- and Q-type channels being enhanced, but to a lesser degree [64]. These data further serve to illustrate how this pro-inflammatory cytokine can potentiate Ca^{2+} entry through multiple mechanisms.

It has also been proposed that the influence of TNF-α on ionic homeostasis extends beyond the plasma membrane channels. Experiments performed on primary cortical neurons have indicated that enhanced inositol 1,4,5 trisphosphate receptor (IP_3R) signaling occurs acutely after TNF-α exposure [66]. These potentiated signals appear to arise from enhanced IP_3R protein expression through TNF-α mediated regulation of a specificity protein-1 (SP-1) binding site found within the IP_3R promoter [67]. Although the exact mechanism for this regulation is currently unknown, it is possible that enhanced IP_3R activity significantly affects gene transcription, dendritic arborization, and/or neuronal firing rates, hence altering neuronal homeostasis [68–70].

In aggregate, TNF-α imparts multiple effects on neuronal signaling and synaptic activity in self-resolving inflammatory responses arising within the setting of a “normally” functioning CNS. The precise contributions and underlying dysfunction of each of these processes in the

genesis and/or progression of neurodegeneration have yet to be clarified. There are significant data, however, implicating TNF-α signaling in the pathogenesis of a number of neurodegenerative diseases, including PD and AD [1–4]. In the remaining sections, we will present the current viewpoints regarding the roles for TNF-α signaling in these debilitating diseases.

2.7 TNF-α in Parkinson's disease

Parkinson's disease is an age–related movement disorder that is characterized clinically by a resting tremor, bradykinesia, and postural instability [71]. The specific loss of dopaminergic neurons in the substantia nigra and striatum underlies the clinical manifestation of this debilitating disease. The correlative presence of inflammatory cytokines in the cerebrospinal fluid (CSF) of PD patients was described by Mogi and colleagues who found that TNF-α levels were enhanced in CSF of those afflicted with the disease [3]. The same group also observed enhanced TNF-α levels in the striatum of patients that had succumbed to PD. Others have reported that TNF-RI levels are elevated in the substantia nigra of PD patients [72], further suggesting altered TNF-α signaling is participating in or a result of PD-related pathogenesis.

Neurotoxicant-based mouse models have been generated as a means to experimentally mimic PD-like neuropathology. Infusion of either the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 6-hydroxydopamine (6-OHDA) induces degeneration of the nigrostriatal pathway and concomitantly enhances the levels of TNF-α within the striatum and substantia nigra [73,74]. Experimental ablation of the TNF-α receptors protects against MPTP-induced dopaminergic neurotoxicity [74]. Separate confirmatory experiments also indicated that the reduction in soluble TNF-α through genetic ablation or through pharmacological methods diminished MPTP [75] and 6-OHDA toxicity [76], indicating that the selective susceptibility of dopaminergic neurons to neurotoxicant injury is at least partially dependent upon intact TNF-α signaling. Other studies have focused on a possible role for TNF-α signaling in the microglial activation observed in PD pathogenesis. The administration of MPTP or 6-OHDA activates these brain-resident immune cells [77,78], and if TNF-α receptor expression is genetically suppressed, microglial activation is absent and MPTP-induced neurotoxicity is significantly blunted [79].

Beyond neurotoxicant models, the transgenic expression of mutant or wild-type proteins associated with familial PD has been employed to model PD *in vitro* and in mice. Alpha-synuclein protein is found in Lewy bodies, the dense intracellular proteinaceous inclusions that are the major pathological hallmark of PD. Fully penetrant familial mutations within the human alpha-synuclein gene locus have been used by several groups to generate transgenic mouse models of the disease, and to study the pathological effects of the encoded mutant protein [80,81]. One such murine PD model utilizing the A53T familial PD linked alpha-synuclein mutation has ascribed inflammatory events as major contributors to the loss of DA neurons [82]. Additionally, the transgenic overexpression of or *in vitro* exposure to the wild-type or mutant alpha-synuclein protein leads to the elicitation of inflammatory responses. For example, Su et al. demonstrated that exposure of microglial cultures to alpha-synuclein protein led to their activation and initiated a pro-inflammatory cytokine cascade preceded by TNF-α expression, suggesting the presence of extracellular alpha-synuclein can lead to neuroinflammation and possibly contribute to PD pathogenesis [83,84].

It should be noted that one of the most challenging aspects of implicating neuroinflammation in human neurological diseases is the fact that therapeutic interventions themselves can produce unintended modulation of the brain inflammatory state. Controversial studies examining levodopa (L-DOPA), which is the primary treatment used to alleviate the symptomology of PD, have indicated that the treatment may enhance pro-

inflammatory signaling. When peripheral blood mononuclear cells obtained from PD patients were treated with L-DOPA, an increase in TNF-α production was observed [85], suggesting that at least a subset of the increases in TNF-α observed in PD patients are due to the administration of the drug and not necessarily due to PD pathogenesis. Conversely, further examination of this process in the 6-OHDA neurotoxicant model of PD has led to the conclusion that L-DOPA does not enhance CNS inflammation *in vivo* [73]. A subset of epidemiological studies have also indicated that the use of non-steroidal anti-inflammatory drugs (NSAIDs), in particular ibuprofen, can reduce the risk of developing PD theoretically by limiting CNS inflammation [86,87]. However, similarly designed studies have failed to find a lack of correlation between ibuprofen use and lowered PD risk [88]. These disparate findings demonstrate that carefully controlled studies performed in the absence of potentially confounding therapeutic interventions, although not easily performed, are needed to clarify the purported links between TNF-α and PD pathogenesis.

An interesting recent development relates to the identification of polymorphisms within the non-coding regions of the TNF-α gene locus that have been associated with altered cytokine expression and increased potential to develop sporadic PD. Genetic analysis of PD patients revealed that the occurrence of a specific allele (−1031C) within the TNF-α promoter was markedly predictive of an earlier onset form of sporadic PD [89]. A similar study that examined patients with early-onset PD indicated that an additional TNF-α gene polymorphism (−308A) may also play a role in PD susceptibility [90]. These studies not only suggest that modulation of TNF-α expression enhances one's risk for the development of PD, but further implicate dysfunctional TNF-α signaling in neurodegeneration.

2.8 TNF-α in Alzheimer's disease

Alzheimer's disease (AD) is an age-dependent neurological disease hallmarked by the formation of amyloid plaques, neurofibrillary tangles, and synaptic demise. Patients afflicted with the disease display deficits in learning, short-term memory, and emotional stability [91]. The prevailing amyloid cascade hypothesis proposes that the accumulation of the fibrillogenic peptide amyloid-beta (Aβ), the major contributor to amyloid plaques, is responsible for the genesis of the disease [92,93]. Dominant mutations in the genes encoding amyloid precursor protein (APP), the parent molecule from which Aβ is derived, and presenilin (PS)-1 and 2, components of the gamma-secretase enzyme complex that proteolytically cleaves APP, have been attributed to a rare (<5%) genetically linked early-onset form of AD. A majority of AD cases arise from other contributing factors of yet unknown genetic and environmental origins. As with other neurodegenerative diseases, neuroinflammation is believed to participate in the progression of AD. Studies examining the sera of AD patients have shown a somewhat weak correlation of enhanced TNF-α levels with disease severity [4]. However, since the levels of inflammatory cytokines typically increase with normal aging, these data may merely be correlative, and not necessarily speak to a contributory role for TNF-α in the disease.

Microglial activation has long been associated with AD pathology. More than two decades ago, the presence of activated microglial cells in close proximity to amyloid plaques was revealed in AD-afflicted brains [94]. The elaboration of heightened microglial activation has been observed as well in several animal models of AD [95,96]. It has been hypothesized that these activated immune cells are in the process of clearing these extracellular deposits. A consequence of increased Aβ exposure is the stimulation of microglial Toll-like receptors and TNF-α expression [97].

The role of TNF-α in the induction and/or progression of AD is currently under study in a number of preclinical models of the disease. Janelsins et al. examined age-related elaboration of inflammatory mediators in the 3xTg-AD mouse model of AD [95]. This

model, developed in the laboratory of Dr. Frank LaFerla, recapitulates not only the amyloid deposits present in AD, but the neurofibrillary tangle pathology as well. 3xTg-AD mice harbor three transgenes: the double mutant APP^{SWE} transgene, a PS^{M146V} knock-in mutation, and a frontal temporal dementia-derived mutant transgene, Tau^{P301L}. Using this model, Janelsins and colleagues discovered a temporally specific enhancement in TNF-α and MCP-1 in the entorhinal cortex. Later, TNF-α was shown to be expressed by microglia and neurons in these mice [98]. This observation was also verified in a singly transgenic APP^{SWE} mouse model [99]. However, the source of the cytokine in the latter study was suggested to be of glial origin. Regardless of cell source, the elaboration of TNF-α occurs during the onset of intraneuronal-associated Aβ accumulation [98], the same time period when deficits in learning and memory initially become evident [100]. Subsequent experiments examined the role of TNF-α over-expression in the 3xTg-AD model, where experimentally enhanced levels of the cytokine generated a neurotoxic environment [98], potentially through enhancement of intraneuronal Aβ. McAlpine et al. recently reported that viral vector-mediated expression of truncated TNF-R constructs in LPS-infused 3xTg-AD mice, as well as 3xTg-AD crosses to TNF-RI knock-out mice, suppresses AD-related amyloid pathology [101]. Interestingly, Liao and colleagues observed that TNF-α increases Aβ generation through regulation of the gamma secretase complex [98,102]. Other studies have suggested that Aβ peptides are produced in both neurons and glia cells following TNF-α exposure [103]. The cyclical process of Astimulation of inflammation and TNF-α signaling, which in turn leads to the generation of new pathogenic Aβ peptides, could produce a potent feed-forward loop (Figure 3). Early detection and intervention at specific points along this cyclical process may be key to disrupting the progressive decline associated with AD.

Because TNF-α signaling has been implicated in AD, the potential clinical impactof broad-based inflammatory and TNF-α signaling interventions has been examined. Similarly to that observed in PD, retrospective analysis of those afflicted with arthritis has suggested that regular users of NSAIDs have a lower risk for the development of AD [104], especially those users who consistently used NSAIDs for more than 24 months [105]. However, a double-blind, placebo-controlled clinical trial has indicated no significant benefit of ibuprofen or low-dose naproxen treatment in halting the cognitive decline or pathology observed in AD [106,107]. TNF-α specific interventions have been evaluated clinically. Open-label pilot studies have examined the effects of etanercept, a TNF-α inhibitor, on the cognitive status of those afflicted with AD [108]. The results indicate that the specific inhibition of TNF-α with perispinal administration of etanercept may alleviate the deficits observed in verbal fluency and aphasia [109]. Such promising results, although garnered through an open-label trial design, provide a rationale for further evaluation of such a TNF-α intervention in larger double-blind clinical trials.

3. Conclusion

The role of TNF-α as a central inflammatory mediator has been shown to extend beyond its activity in classical inflammatory responses and is now heavily regarded as a major regulator of complex physiologic processes within the CNS. Its documented signaling cascades elicit a multitude of effects on cellular viability, ionic homeostasis, and synaptic plasticity. Furthermore, dysregulated TNF-α signaling has been implicated in the initiation and/or progression of a number of human diseases. Only through careful *in vivo* dissection of the complex pathways altered by TNF-α signaling and their disease-stage contribution to pathogenesis will we acquire a better understanding of TNF-α's varied roles in the loss of neuronal viability, motor function, and cognition associated with these debilitating diseases. Such information will undoubtedly provide valuable guidance for rational therapeutic

design, treatment regimen, and target specificity as a means to safely and effectively remedy dysfunctional signaling attributed to TNF-α action in a degenerating CNS.

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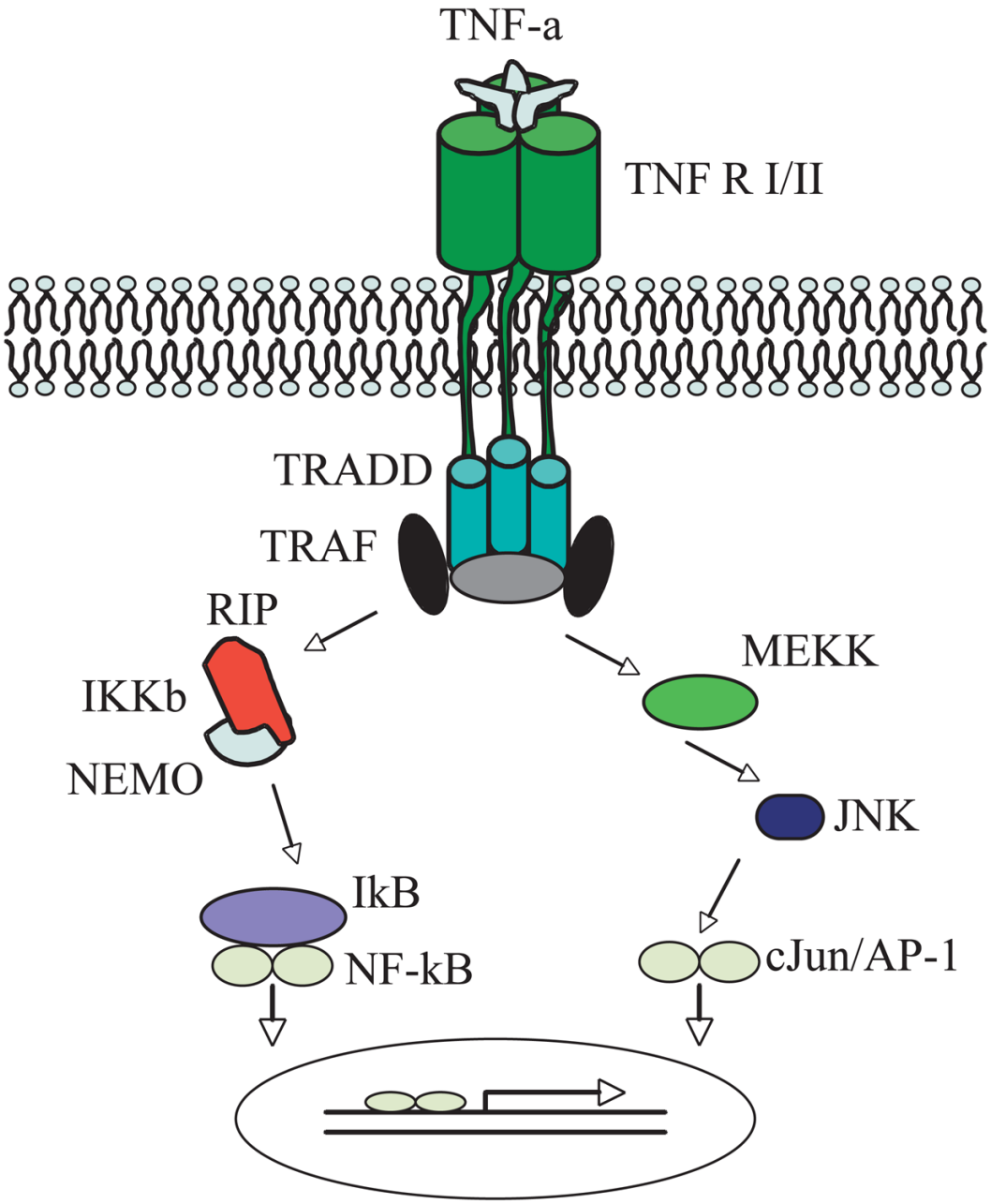

Figure 1. TNF-α receptor signaling cascade

Binding of TNF-α to either of its cognate receptor subtypes can initiate apoptosis through TRADD domain activation or lead to the initiation of the NFκB and JNK signaling pathways. These signaling cascades can then result in activation/repression of key transcriptional targets and/or alterations in cellular physiology and viability.

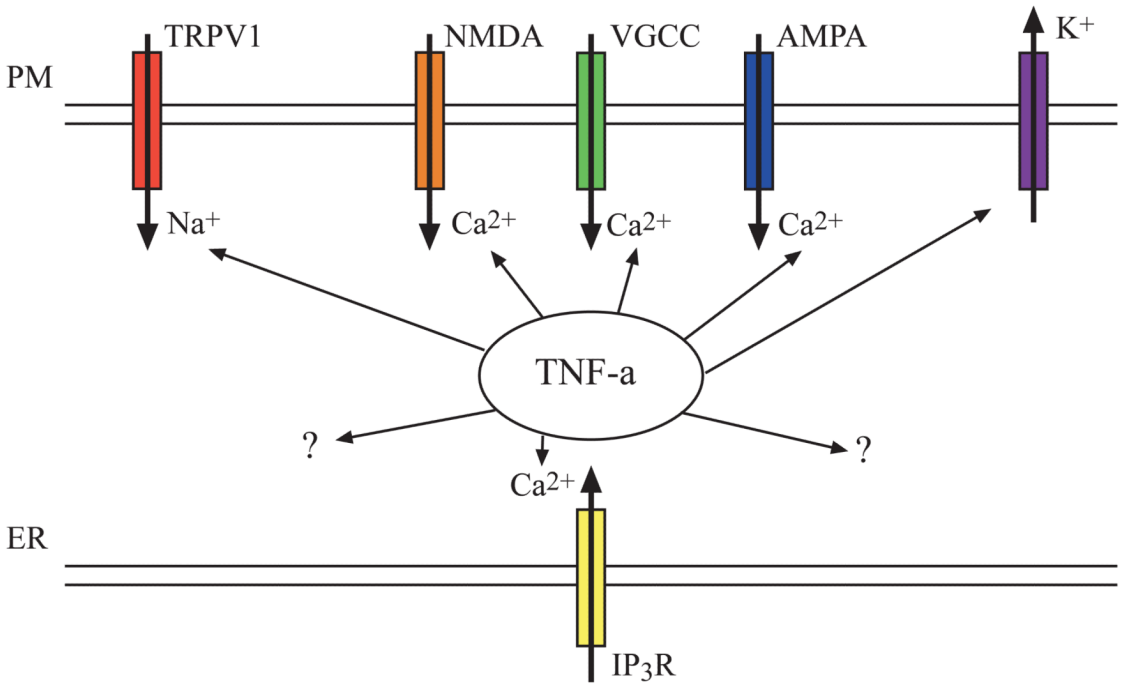

Figure 2. TNF-α can modulate the activity of a number of neuronal ion channels

The activation of signaling cascades downstream of TNF-R activation leads to several alterations in ionic homeostasis. The known effects of the cytokine on specific neuronal channels are depicted.

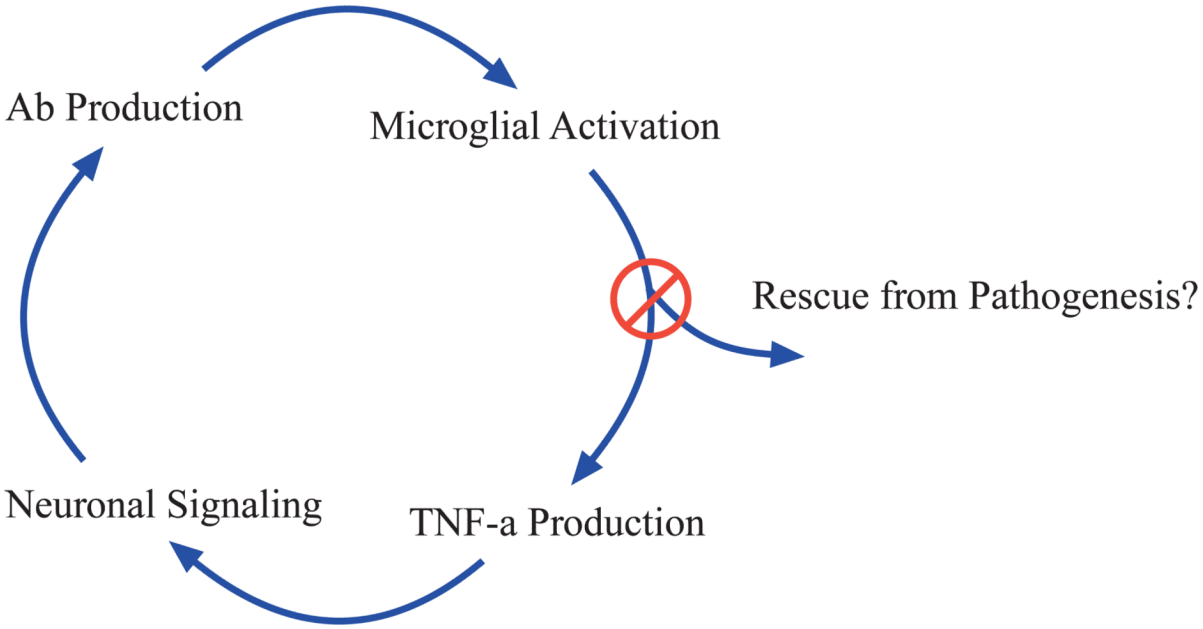

Figure 3. Proposed feed-forward loop underlying AD pathogenesis

The accumulation of Aβ can induce microglial activation and the production of TNF-α. Furthermore, TNF-α has been shown to elicit several neuronal responses, including the heightened generation of Aβ. This feed-forward process is shown in a loop diagram. The resolution of which, through TNF-α signaling interventions, could result in the amelioration of Alzheimer's disease pathology.