

Role of Tumor Necrosis Factor in Neurodegeneration

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Abstract

Neurodegeneration is characterized by death of nerve cells through various mechanisms such as injury, infection, dysregulated cellular mechanisms etc. many of these aspects are mediated by inflammation. Usually inflammation is a protective response, but chronic inflammation leads to diseased state which is true for many neurodegenerative diseases. TNF- α mediates neuroinflammation along with upregulation of other pro-inflammatory cytokines such as interleukins (IL-1, IL-6) and interferons (IFN- γ). Nerve cell death may be due to apoptosis, necroptosis, cytotoxicity, excitotoxicity and many other mechanisms. This review summarizes about various neurodegenerative diseases that are initiated by neuroinflammation caused by TNF- α and molecular mechanisms of signaling that are involved in regulation of neuronal cell death.

Keywords: Tumor Necrosis Factor- α ; Cytokines; Interferons; Neurodegeneration; Lipopolysaccharides; TNFR1; TNFR2; DAMPs; Apoptosis; Necroptosis; Oxidative Stress; Excitotoxicity

Introduction

Chronic neuroinflammation is the major cause of neurodegenerative diseases in the central nervous system (CNS). Tumor necrosis factor (TNF) is one of the major pro-inflammatory cytokines which initiates and regulates cascade of signals during inflammation [1]. Neuroinflammation is induced by many factors like Lipopolysaccharides (LPS), unusual intra or intercellular protein accumulations, viruses, mitogens, prions, 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1, 2, 3, 6 - tetrahydropyridine (MPTP), HIV coat protein gp120, ischemia, etc [2,3]. Factors causing inflammatory responses initially activate toll-like receptors (TLR) present on the microglia which leads to the activation of microglia (regarded as immune cells of brain) and produces pro-inflammatory cytokines (IL-1, IL-6, TNF- α). Not only microglia, it is also suggested that the neurons and astroglial cells also produce cytokines [4]. TNF- α is one of the major proinflammatory cytokines which has a crucial role in regulation of inflammatory responses, it has two forms membrane TNF- α (mTNF- α) and soluble TNF- α (sTNF- α) [5]. Although TNF- α and other cytokines are initially released for neuroprotection, however, it becomes toxic in the later stages of inflammation. A number of immune functions such as phagocytosis, production of cytotoxic (eicosanoids, NO) and neurotrophic (NGF, BDNF) factors is observed when CNS is stimulated subsequent to microglial activation and may serve as a causative factor for uncontrolled inflammatory responses [6].

There are many ways by which a neuron dies such as over-sensitization, apoptosis, necroptosis etc. Over-sensitization is caused by an increase in the levels of receptors of a particular neurotransmitter, for instance, number of Glutamate receptors go up when TNF- α levels are increased, this leads to increased sensitivity to Glutamate [7]. NF- κ B (Nuclear factor kappa B) is a transcription factor and regulates the functions of TNF- α . NF- κ B usually has a role in normal cell survival and protection of cell by secreting pro-inflammatory cytokines

such as IL-1, IL-6, IFN- γ and TNF- α . TNF- α also activates apoptotic and necroptotic pathways [8]. TNF- α is the most potent activator of NF- κ B, but NF- κ B itself is a transcription factor which induces production of TNF- α and fellow cytokines. NF- κ B also regulates other mediators of inflammatory pathways such as chemokines, adhesion molecules, enzymes and kinases [9]. Initially, NF- κ B gets activated in response to many other stimuli including TNF- α such as other inflammatory cytokines, stress, fatty acids, reactive oxygen species (ROS), reactive nitrogen species (RNS), high glucose, UV radiation, cigarette smoking, allergy, and other disease causing factors [10,11].

Receptors involved in TNF- α signaling

Two major cell surface receptors are known to mediate the biological effects of TNF- α , the p55 TNF receptor (TNFR1) and the p75 TNF receptor (TNFR2). The location of TNFR1 and TNFR2 genes are 12p13.31 and 1p36.22 respectively [12]. Both the receptors belong to a same superfamily which has Cysteine rich extracellular domains, but intracellular domains differ significantly, suggesting that distinct signaling pathways emanate from two receptors. Both TNFR1 and TNFR2 have soluble forms; these soluble forms compete with membrane bound forms and neutralize the effect of TNF- α . But, the soluble forms are also regarded as stabilizers of TNF- α , they also prevent TNF- α from degradation [13,14].

TNFR1 is expressed in all the cells which are nucleated including neurons. Its expression is low and is generally involved in TNF mediated effects. It also signals for other factors like Fibroblast growth factor (FGF) [15], both soluble TNF- α (sTNF- α) and membrane TNF- α (mTNF- α) have potential to trigger TNFR1 [10]. TNFR1 is a mediator for TNF- α induced cytotoxicity and apoptosis [8].

TNFR2 is also expressed in brain cells and has got a higher affinity towards TNF than TNFR1. Only mTNF- α is shown to activate TNFR2 [5]. TNFR2 is found to enhance TNFR1 mediated apoptosis. Some studies suggest TNFR1 and TNFR2 may play contrasting roles that may be either neuroprotective or may be neurodegenerative [16]. The molecular cascades involved in TNFR1 and TNFR2 signaling is presented in figure 1.

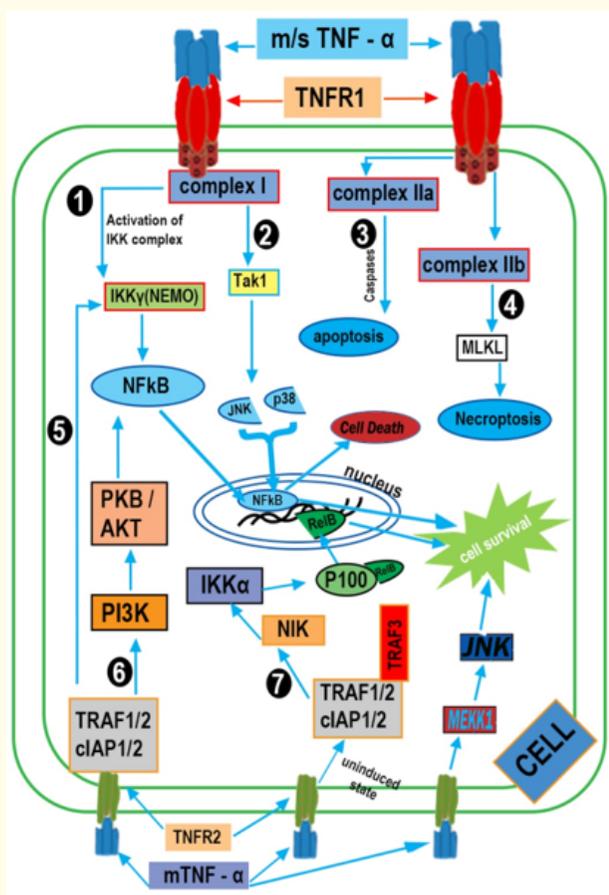


Figure 1: Summary of events in TNF- α signaling via TNFR1 and TNFR2 receptors.

Signaling pathways of TNFRs

TNFR1 signaling

When TNF- α binds to TNFR1 downstream signaling process starts and TNFR1 gets activated and results in the activation of TNF receptor-associated death domain adaptor protein (TRADD). Depending on the cellular circumstances the TRADD-TNFR1 association permits recruitment of distinct signaling complexes complex I and complex II [17,18].

Complex I is composed of TRADD, TNF receptor associated proteins 2/5 (TRAF2/5), cellular inhibitor-of apoptosis proteins 1/2 (c-IAP 1/2), ubiquitin-conjugating enzyme 13 (Ubc 13), and receptor interacting protein-1 (RIP-1). Subsequently the RIP-1 is poly-ubiquitinated [19,20]. This activated complex in turn activates I κ B kinase (IKK) complex. The IKK complex acts as regulatory sub unit of IKK kinase γ or NF- κ B essential modulator (NOME). Phosphorylation of I κ B by IKK activates NF- κ B which then translocate to nucleus [19,21]. Complex I may also go through a pathway which activates transforming growth factor β -activated kinase 1 (TAK1) complex. TAK1 activation is necessary for p38 or JNK kinase pathways. Signaling via these two pathways leads to production of pro-inflammatory cytokines, chemokines, COX-2, anti-apoptotic factors (cIAPs, TRAFs, Bcl-2, c-FLIPs) [21,22]. cFLIP (cellular FLICE-like inhibitory protein) is a Caspase 8 inhibitor. cFLIP, produced by TNF- α mediated NF- κ B signaling is necessary to suppress apoptotic action of caspases and increase cell survival probability [22]. When NF- κ B signaling fails, TNFR1 will recruit complex IIa to initiate apoptosis (Figure 1). Complex II consists of proteins such as TRADD, RIP1, TRAF2 (TNFR Associated Factor), and Fas-associated death domain (FADD) and pre-caspase 8. FADD and caspase-8 are essential for initiating apoptosis [23].

Apart from complex IIa there is also complex IIb which mediates programmed necrosis or necroptosis. This pathway is activated when there is no apoptosis. Complex IIb contains all the proteins of Complex IIa, pre-caspase 8 and an extra protein RIP3 is present which is activated by RIP1 kinase and MLKL (mixed lineage kinase domain-like protein) [8].

TNFR2 signaling

There is a lot of similarity between TNFR1 and TNFR2 signaling and proteins involved in molecular cascades downstream. Like TNFR1, the TNFR2 also acts via different pathways to increase NF- κ B mediated production of pro-inflammatory cytokines and anti-apoptotic factors. TNFR2 binds only to membrane TNF- α (mTNF- α) and does not possess death domain [5], this relates to TNFR2 only acting in cell survival pathways. Major pathway in TNFR2 signaling is initiated by trimerization of TNFR2 upon binding of mTNF- α , which leads to enrollment of TRAF2 and subsequent activation of TRAF1, cIAP1, and cIAP2. Formation of this protein complex leads to activation of NF- κ B through IKK dependent pathway [24] (Figure 1).

NF- κ B is also activated via phosphoinositide 3 - kinases (PI3K) - protein kinase B/serine-threonine kinase (PKB/Akt) signaling pathway. After that NF- κ B is translocated into nucleus to initiate transcription [25].

Another major pathway which is independent of IKK β and IKK γ (subunits of IKK complex) is also reported, it depends on IKK α and NIK (NF- κ B inducing kinase). This pathway involves TRAF3 in addition to TRAF1/2 and cIAP1/2, TRAF3 recruits the TRAF2-cIAP1/2 complex to NIK [26]. This pathway is called non-canonical as it is independent of IKK β and IKK γ .

JNK (c-jun N-terminal kinase) or p38 MAP kinase dependent pathways are also reported in TNFR2 signaling. In this pathway the TNFR2 recruits TRAF1/2/3 and cIAP1/2, these molecules activates MEKK1 (MAP Kinase Protein) by binding to it. Activated MEKK1 now phosphorylates JNKK1; JNKK1 further promotes downstream signaling via JNK which promotes cell survival [27].

The JNK pathway in here is also mediated by TRAF1/2/3 and cIAP1/2 all these proteins bind to the MEKK1 protein, this further phosphorylates JNKK1 (not shown in figure) which further activates JNK and it mediates cell survival.

Major causes of neurodegeneration involving TNF- α mediated inflammatory response

Oxidative stress: Oxidative stress is considered to be one of the major issues created by TNF- α . It is viewed as both cause and consequence of neuroinflammation. Both reactive oxygen species (ROS) and reactive nitrogen species (RNS) are generated either through TNF- α signaling or may enter the cell from outside. Major ROS/RNS are (Hydrogen Peroxide) H₂O₂ and Nitric Oxide (NO). H₂O₂ is produced

by mitochondria by NADPH oxidase (NOX). Initially a superoxide anion (O_2^-) is produced and disproportionation leads to production of H_2O_2 . Similarly, NO is also produced by using enzyme inducible nitric oxide synthase (iNOS). Finally, the ROS/RNS mediated signaling causes downstream expression of transcription factors such as NF- κ B, to induce the production of cytokines, chemokines and other ROS/RNS generating enzymes. TNF- α induced oxidative stress is extensively reviewed in many articles [28].

Excitotoxicity/over-sensitization: Excitotoxicity/Over-sensitization can be explained using the example of Glutamate neurotransmitter. Astrocytes, Blood-Brain Barrier (BBB) and neurons are found to regulate levels of Glutamate in extra cellular fluid (ECF) of the CNS [29]. In one such pathway, NF- κ B mediated regulation of TNF- α is shown to have a role in decreased production of excitatory amino acid transporters (EAATs), a major transporter of Glutamate found in the CNS. This infers, increased levels of TNF- α leads to the Over-sensitization and eventually leading to death of neuron [7,29].

Damage associated molecular patterns (DAMPs) and alarmins: Molecules released from dying pathogens, necrotic tissues (not apoptotic tissues), and damaged areas that are recognized by immune system as a signal for rapid response. Molecules released from endogenous necrotic tissues are called Alarmins. DAMPs and alarmins are recognized by TLRs and initiates cascades of reactions below the line and cause production of TNF- α which eventually leads to neuroinflammation [28].

Apoptosis and necroptosis: Apoptosis is a form of programmed cell death mediated by caspases. Morphological features of apoptosis include expulsion of phosphatidylserine (PtdSer) to the outer side of the plasma membrane, chromatin condensation and DNA cleavage. Exposure of PtdSer to surface signals macrophages and other phagocytic cells to clear the debris. In contrast Necroptosis is a form of Necrosis where plasma membrane permeability increases and organelle swells, this process is not mediated by caspases. Both apoptosis and necroptosis are reported during activation of TNF- α mediated pathway in the CNS [8].

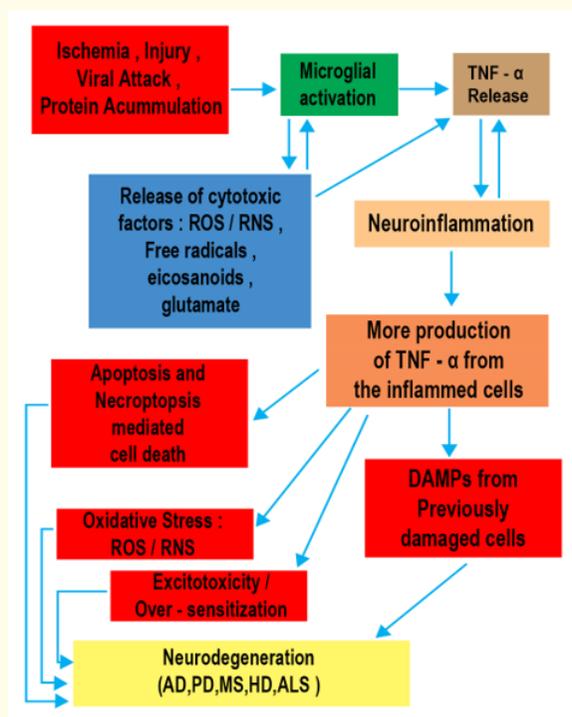


Figure 2: Outline of pathways leading to neurodegeneration mediated by TNF- α .

Role of TNF- α in some major neurodegenerative diseases

Alzheimer's Diseases (AD), Parkinson's Disease (PD), Multiple Sclerosis (MS), Cerebral Ischemia (CI) and Amyotrophic Lateral Sclerosis (ALS), traumatic brain injury (TBI), epilepsy are some of the major Neurodegenerative diseases where TNF- α is directly involved. Apart from these major diseases some other less common diseases like Creutzfeldt-Jakob's disease (CJD), Huntington's disease (HD), lysosomal storage diseases (LSDs), are also seen in individuals where TNF- α act as a prime factor in progression of that particular disease. We are discussing involvement of TNF- α and its receptors only in few major neurodegenerative diseases.

Alzheimer's disease (AD)

AD is one of the most common diseases in aged individuals and has increased at an alarming rate due to increase in lifespan of individuals [30]. Neuropathological studies have suggested that neuroinflammation is an early event in pathogenesis and history of AD. AD is a complex, persistent neurodegenerative disease classified by impaired cognitive function and also characterized by the presence of intracellular Amyloid- β (A β) plaques and intercellular Neurofibrillary Tangles (NFTs) in brain tissue [31]. Inflammation is considered to be one final common pathway through which Neuritic plaques and NFTs manifest their neurodegenerative effects. Traumatic injury stimulating inflammatory response is also a major risk factor for developing AD [32].

The role of TNF- α in AD is much discussed and debated. Upregulation of many pro-inflammatory cytokines, complement proteins are seen in AD brain. TNF- α is majorly found at regions of A β plaques and NFTs in AD brains, it causes neuronal damage by over stimulating the immune system. There are three genes which seem to increase A β production in early onset AD brains, the amyloid- β , presenilin-1, presenilin-2; this A β seems to activate microglia and astrocytes to secrete major pro-inflammatory cytokines including TNF- α [33,34]. There is also other apolipoprotein E (APOE) which is synthesized and secreted by microglia and astrocytes, and their secretion is stimulated by TNF- α , fellow cytokines [35]. Numerous studies have shown that upregulation of APOE may increase A β deposition and further oxidation by free radicals of A β may lead to formation of neurotoxic NFTs which further leads to over-stimulation of neurons. TNF- α which is released mainly by microglia and astrocytes, induces fellow cells through NF- κ B pathway, further to secrete more amounts of TNF- α , cytokines, APOE. TNF- α also induce production of cyclo-oxygenase 2 (COX2), which increases the levels of free radicals [36] and as stated above free radicals oxidize A β to form plaques and they also oxidize NFTs. Receptors, TNFR1 and TNFR2 play a major role with respect to TNF- α action in AD. Mainly TNFR1 mediates death signals as carries an intracellular death domain, in contrast TNFR2 don't have a death domain. Further, it has been reported that TNF- α has a higher affinity to TNFR1 and less affinity to TNFR2 [37].

Parkinson's disease

Parkinson's disease (PD) is considered as the second most common neurodegenerative disease after AD. It is caused by the progressive loss of dopaminergic neurons (DA) in substantia nigra pars compacta (SNpc) region of the brain. One of the main characteristic features of PD is loss of motor function and control of movement. The pathological attributes of this neurodegenerative disorder is accumulation of α -synuclein intracellularly leading to formation of Lewy bodies and loss of Dopamine. 10 - 15% of PD are early onset PD, which are familial, the rest are late onset or sporadic [38]. Familial PD may be of recessive or dominant in nature. Recessive PD is associated with mutations Parkin, DJ-1 and PINK1 (phosphatase and tensin homolog [PTEN]-induced putative kinase-1 [39]. Whereas dominant PD includes mutations in PARK1/SNCA (α -synuclein) and PARK8/LRRK2 (leucine-rich repeat kinase 2). In sporadic PD microglia are activated by transcription of STAT (signal transducer and activator of transcription), which in turn produce TNF- α and other pro-inflammatory cytokines. These cytokines further activate NOX and iNOS to produce ROS and NOS respectively. As said earlier ROS/NOS are leading factors of neuroinflammation, which eventually leads to neurodegeneration [40].

Recombinant Adeno-associated viruses having α -Synuclein are made to infect substantia nigra of mouse which resulted in over expression of TNF- α [41]. NF- κ B which is shown to have a neuroprotective function also plays a major role in TNF- α mediated degeneration of

dopaminergic neurons. A study supports this idea and showed an increased level of TNFR1 in substantia nigra of PD patients. Nagatsu, *et al.* suggested that increased levels of pro-inflammatory cytokines (TNF- α , IL-1, IL-6, IFN- γ), decreased levels of neurotrophins (NGF, BDNF), and also changes in levels of apoptotic factors are seen in nigro-striatal region of brain when infected with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or by 6-hydroxydopamine (6-OHDA) [42].

Multiple sclerosis (MS)

MS is a demyelinating disease in which insulating covers of nerve cells known as myelin sheath in the CNS are damaged. The damage leads to decreased communication between parts of nervous system which may lead to symptoms such as double vision, trouble with sensation and coordination. MS takes several forms, with new symptoms either occurring in isolated attacks (relapsing forms) or building up over time (progressive forms) [43]. Death of Oligodendrocytes leads to reduced or no myelin production which replaces damaged myelin [44]. TNF- α knockout experimental autoimmune encephalomyelitis (EAE) mice show increased inflammation, decreased life span and demyelination [45] suggesting a possible role of TNF- α in increasing inflammatory responses as well as demyelination of nerve fibers thereby facilitating MS.

TNF- α has got both advantageous and damaging effects which depends completely on activation of either TNFR1 or TNFR2. If TNFR1 is activated to undergo downstream signaling processes it mediates apoptosis of oligodendrocyte and demyelination. In contrast TNFR2 signaling mediates re-myelination and oligodendrocyte precursor cell proliferation [44].

Amyotrophic lateral sclerosis

Amyotrophic Lateral Sclerosis (ALS) also known as Motor Neuron Disease (MND) is a specific neurodegenerative disease which causes death of motor neurons controlling voluntary movements. ALS symptoms include stiffened muscles, muscle twitching and in due course of time the situation worsens as almost all skeletal muscles are paralyzed [46]. Almost 90% of cases arise spontaneously and only 10% cases involve genetic mutations which are inherited as a dominant trait [47]. There are many genes which are related to ALS and include the well-known Cu²⁺/Zn²⁺ superoxide dismutase (SOD1) gene and twelve other genes (extensively reviewed in Massimo Tortarolo, *et al* [47]. All the mutant genes work in the same manner which ultimately leads to pathogenesis of ALS. Motor neuron degeneration is a slow in which also involves non-neuronal cells of CNS (microglia), PNS and immune cells [46].

TNF- α is considered one of the major pro-inflammatory cytokines which takes the credit of motor neuron death in ALS patients and animal models. TNFR1 and TNFR2 are known to mediate the signaling of TNF- α . In contrast to AD, PD and MS where TNFR1 is the major cause of cell death, in ALS activation of TNFR2 are mainly involved in cell death [48].

Cerebral ischemia

Cerebral Ischemia is a condition when blood vessel supplying blood to parts of brain gets obstructed, which leads to lack of supply of oxygen, metabolites and nutrients to that part of brain. This causes damage to the cells in the affected and surrounding area. TNF- α production is substantially elevated in the affected region [49]. Similar to diseases discussed previously removal of TNF- α signaling or amplifying TNF- α signaling leads to ischemic stroke/cerebral ischemia. However, review by Yun Dong, *et al.* suggests that TNFR2 is more potent in causing increased neurodegeneration than TNFR1 in cerebral ischemia [27].

Targeting of TNFR2 via agonists for treating neurodegenerative diseases

As shown in figure 2, the pathways leading to neurodegeneration are mainly dependent on TNF- α and the pathways are coordinated by TNFRs. As described in section 2.1 the TNFR1 and TNFR2 are the two TNF- α receptors, they act contrastingly with respect to each other, the TNFR1 promotes neurotoxicity whereas TNFR2 leads to pathways which are neuroprotective in function [21,27]. *In vitro* studies have established that TNFR2 can protect the neurons from excitotoxic insults and also promotes oligodendrocyte regeneration [44].

One of the major neurodegenerative diseases is the Alzheimer's disease (AD). AD is predominantly seen in aged individuals. Both TNFR1 and TNFR2 are major therapeutic targets used to prevent neuronal cell death [37]. Experiments conducted by Fischer, *et al.* provided some interesting results which are in favor of this section. They constructed a soluble human TNFR2 agonist TNC-scTNF_{R2}. The molecule has the ability to mimic mTNF- α . The experiment briefly included inducing oxidative stress in the neuronal cells and treating them with the agonist TNC-scTNF_{R2}. This resulted in survival of some cells. Similar studies were also conducted by Dong, *et al.* in collaboration with Fischer, *et al.* The molecule used by them is EHD2-scTNF_{R2}, this also produced similar result [37,50]. These results show us that targeting and activation of TNFR2 in future by some similar and more efficient molecules may cure Alzheimer's disease as well as other neurodegenerative diseases.

Conclusion

TNF- α is a major pro-inflammatory cytokine which plays a pivotal role in causing neuroinflammation. This neuroinflammation leads to neurodegeneration. As of now many studies have suggested that TNF- α modulation shows decreased neurodegeneration. Familial/early onset neurodegenerative diseases are less in number when compared late-onset ones. This suggests involvement of many environmental factors in aggravating neuroinflammation. It has always been complicated to understand whether TNF- α initiates neuroinflammation or vice versa. More researches are needed to formulate drugs targeting metabolites that are part of TNF- α mediated pathway, which can serve in long run as potential treatment strategy in management of many neurological disorders.

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Conflict of Interest

The author (editor) declares no conflict of interest, financial or otherwise.

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