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Review

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.

Contents

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 chronic neuroinflammation [1–4], indicating

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that 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. Tumor necrosis factor-alpha

TNF-α was first described by Carswell et al. 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.

3. Tumor necrosis factor-alpha signaling

TNF-α interacts with two cognate receptors: p55 (TNF-RI) and p75 (TNF-RII) (Fig. 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

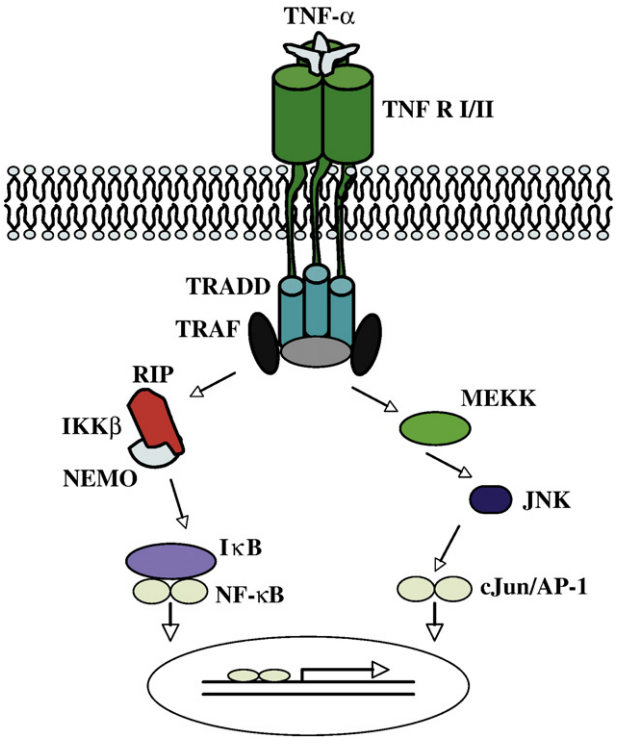

Fig. 1. TNF-α receptor signaling cascade. Binding of TNF-α to either of its cognate receptor subtypes can initiate apoptosis through TRADD domain activation or lead to the initiation of the NFκB and JNK signaling pathways. These signaling cascades can then result in activation/repression of key transcriptional targets and/or alterations in cellular physiology and viability.