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Chapter

Tumor Necrosis Factor Alpha: A Major Cytokine of Brain Neuroinflammation

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Abstract

Tumor necrosis factor (TNF) is one of the most extensively studied cytokine with about 19 distinct superfamily members and many more to be found. Prominent among these members is tumor necrosis factor alpha (TNF-α) that is known to be a potent promoter of inflammation, as well as many normal physiological functions in homeostasis and health and antimicrobial immunity. Nuclear factor kappa-light-chain enhancer of activated B cells (NFκB) is one of the most important transcription factors that activate transcription of many proinflammatory genes, and the unraveling of TNF-α induced NFκB activation forms the foundation of TNF-α as major cytokine of neuroinflammation. This review discusses summary of literature on unique role of TNF-α in neuroinflammation and various agents that mediate neuroinflammation via TNF-α modulation.

Keywords: tumor necrosis factor, tumor necrosis factor alpha, neuroinflammation, cytokine, brain, inflammation

1. Introduction

Tumor necrosis factor (TNF) alpha is one of the first discovered cytokines shown by Carswell [1] in 1975 and was named for tumor regression activity induced in the serum of mice treated with *Serratia marcescens* polysaccharide [2]. Cytokines are low-molecular-weight peptides secreted by activated immune cells as well as stromal cells and exerting biological activities through binding to cognate receptors on cell surface. Cytokines are produced by a number of cell types, predominantly leukocytes that regulate a number of physiological and pathological functions including innate immunity, acquired immunity, and a plethora of inflammatory responses [3]. Cytokines excite or hinder the generation, propagation, and differentiation of different associated target cells positive on antigen induction, thus leading to mediation in the activity of diverse other cells involved in the immune response especially the more pronounced macrophages, mast cells, B cells, T cells, and natural killer (NK) cells. Thus, cytokine is regarded as secreted proteins with growth, differentiation, and activation functions that regulate and determine the nature of immune responses [4]. The broad classification of cytokines are termed in a group as follows: interleukin (IL), interferon (IFN), tumor necrosis factor (TNF), colony stimulating factor (CSF), and chemokine and growth factor (GF), and these exerts biological functions through action mode and characteristics as paracrine,

autocrine, and endocrine. TNF being one of the prominent cytokine has about 19 different members of the TNF superfamily that includes tumor necrosis factor alpha (TNF-α), tumor necrosis factor beta (TNF-β), TNF-related weak inducer of apoptosis (TWEAK), TNF-related apoptosis-inducing ligand (TRAIL), lymphotoxin-β (LT- β), CD40L, CD30L, 4-1BBL, CD27L, glucocorticoid-induced TND receptor ligand (GITRL), fibroblast-associated ligand (FasL), OX40 ligand (OX40L), LIGHT, A proliferation-inducing ligand (APRIL), B-cell-activating factor (BAFF), receptor activator of NFκB ligand (RANKL), vascular endothelial cell-growth inhibitor (VEGI), and ectodysplasin A ((EDA)–A1, EDA-A2) [2].

TNF-α is a potent mediator of inflammation, as well as many normal physiological functions in homeostasis and health and antimicrobial immunity [5]. Inflammation is a classical host defense response of vascularized living tissue to infection and injury, and in the central nervous system (CNS), the term neuroinflammation is used to denote cellular and inflammatory responses of vascularized neuronal tissue through activation of resident cells in the brain (microglia, astrocytes, and endothelial cells), the recruitment of blood-derived leukocytes including neutrophils, lymphocytes, and macrophages, and a plethora of humoral factors [6, 7]. More appropriately, neuroinflammation is a term used to denote inflammation associated with the brain and is characterized by the activation of microglia and expression of major inflammatory mediators without typical features of peripheral inflammation such as edema and neutrophil infiltration [8]. Neuroinflammation in the brain supposedly has a positive effect such as increasing blood flow and removal of damaged tissue by phagocytosis, but in a disease state, the resulting inappropriate inflammation caused negative effects which by far out weight the positive effect [6].

Nuclear factor kappa-light-chain enhancer of activated B cells (NFκB) otherwise called nuclear factor kappa B is a heterodimer and one of the most important transcription factors that activate transcription of many proinflammatory genes. It is well documented that TNF-α induces at least five different types of signals that include activation of NFκB, apoptosis pathways, extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase (p38MAPK), and c-Jun N-terminal kinase (JNK) [2]. These biological functions of TNF-α makes its role in neuroinflammation critically prominent. It is therefore expedient to elucidate and expand the rational basis of TNF-α as major cytokine of neuroinflammation. Hence, this review discusses summary of literature on unique role of TNF-α in neuroinflammation and various agents that mediate neuroinflammation via TNF-α modulation.

2. Neuroinflammation

Microglia being major immune cells involved in defense in the central nervous system, its activation is considered to be the hallmark of neuroinflammation [7, 9]. Activation of microglia cells constitutes the first key acute response in the brain to external aggression such as acute brain ischemia, traumatic brain injury, or microbial pathogen, and this microglial activation is coupled with subsequent activation of blood-borne monocytes/macrophages to yield a full-blown neuroinflammatory thick rim around ischemia infarct that becomes observable after 1 week in both human and animal models [10]. Microglia in the CNS constitutes 5–15% of total brain population; having share common precursor with peripheral macrophages, they produced transient inflammatory changes like macrophages such as phagocytosis, inflammatory cytokine production, and antigen presentation, normally returning to their basal state when the activation stimulus is resolved [11]. In a

disease state such as in the onset of focal cerebral ischemia or traumatic brain injury, however, the microglia response becomes inappropriately more reactive and exaggerated to produce plethora of inflammatory mediators that trigger apoptosis and exaggerate neuronal damage [12]. Therefore, microglia/macrophages are the key immune cells concerned with the protection of brain against injury. Their architectural and functional changes are linked with the liberation of injury signals induced by pathology. These cells are usually responsible for clearance of demised neural cells and allow for restoration of lost neuronal functions. However, when markedly activated by the damage-associated molecular patterns subsequent to a disease state, they can generate a huge amount of proinflammatory cytokines that are capable of interrupting neural cells and the blood-brain barrier, and manipulate neurogenesis [9].

The primary function of microglia in the brain is to control any external aggression and neutralize its effect by a process of phagocytosis, which is a chronologically multistep system including oriented gradient motility (chemotaxis); identification of alien foreign agents by membrane lectins and receptors (recognition); encompassing flow round the injurious foreign agents into a vacuole/phagosome (engulfment); unraveling of intracellular secretor pools (granules); and liberation of innate antibiotics and enzymes into the phagosome, generation of reactive oxygen species by an intricate enzymatic system sequestrated on the phagocyte membrane and/or reactive nitrogen species by an inducible nitric oxide synthase, and decapitating and digestion of engulfed foreign substance in the multifaceted phagolysosomal medium (microbial killing) [13]. Therefore, there are four important events of phagocytosis: chemotaxis, recognition, engulfment, and microbial killing.

Chemotaxis is the immediate restricted, valuable host inflammatory reaction that is initiated by local tenant macrophages, demised cells and tissues, plasma factors, and microbial products. Specifically, the closely generated factors of inflammation (cytokines, activated complement protein, kinins, etc.) and microbial factors construct chemotactic gradients, alter endothelial cell membrane receptors, and encourage decrease of the blood flow. Blood-borne monocytes/macrophages that are rolling along the endothelial surface act in response to the chemotactic and cell-mediated signals and are primarily activated to definitely attach to the endothelium by way of their membrane integrins; the second pace is transendothelial migration, denoted as diapedesis, followed by tilting motility toward the inflammatory site (chemotaxis) [13].

Recognition involves identifying and attachment of particle to be ingested by the microglia/phagocytes. There are two methods of recognition: opsonin/opsonin dependent/receptor mediated and non-opsonin/opsonin independent. Opsonin/opsonin dependent is where microglia/phagocytes recognize pathogens via their membrane receptors for opsonins (e.g., complement factors C3b and iC3b and Fc component of immunoglobulins), which are present on the microbial surface, while non-opsonin/opsonin independent is where microglia/phagocytes recognize pathogens via microbial and phagocyte lectins [13]. Because microglia/phagocytes express high-affinity receptors for opsonin, the term opsonization is used to indicate a process, whereby injurious foreign particle becomes coated with substance, thereby enhancing its recognition by leukocyte and making it more open to phagocytosis. As aforementioned, the injurious foreign agents or microbes are usually opsonized by specific protein substances such as immunoglobulin G (IgG) antibodies, breakdown product of compliment (C3b), and fibrinogen all of which phagocytes express high-affinity receptors.

Engulfment refers to microglia/phagocyte extension of cytoplasm (pseudopods) flow around the injurious foreign agents or microbes after its binding with

phagocyte and subsequent pinches off to form vesicles (phagosome) that enclose the injurious foreign agents or microbes. Phagocyte extensions (pseudopods) finally engulf the injurious foreign agent or microbe in a vacuole and trigger the activation of two functions: the release of granule contents into the phagosome and the oxidative burst. Coiling engulfment is the most frequent unusual uptake: unilateral pseudopods wrap around the microorganism in multiple turns, giving rise to largely self-apposed pseudopodial surfaces [13].

Microbial killing can be achieved through oxygen-dependent or oxygen-independent/non-oxygen-dependent method of pathogen or injurious agent killing. Oxygen dependent involves the use free radicals. A free radical is clearly referred to as atom or molecule having one or more unpaired electrons in valence shell or outer orbit and is competent for autonomous survival [14]. The strange quantities of odd electron(s) possess by a free radical make it unbalanced, short lived, and extremely reactive. This high reactivity makes free radical exert a pull on electrons from further compounds to reach steadiness. The newly pulled attacked molecule loses its electron and becomes a free radical itself, opening a chain of feedback cascade of reaction. Free radicals/oxidants derived from both endogenous sources and exogenous sources have gained importance in the field of biology due to their central role in various physiological conditions as well as their implication in a diverse range of diseases. They include reactive oxygen species (ROS) which are hydroxyl radicals ($^{\cdot}OH$), superoxide (O_2^-), hydrogen peroxide (H_2O_2), and reactive nitrogen species (RNS) which are nitric oxide (NO) and peroxynitrite ($OONO^-$). At reasonable or little concentrations, ROS/RNS encompasses desirable effects and engage in a variety of physiological purposes such as in immune function (i.e., guard in opposition to pathogenic microorganisms), in certain cellular signaling pathways, in mitogenic reaction, and in redox directive. Conversely, at excessively elevated concentrations, both ROS and RNS lead to oxidative stress and nitrosative stress, respectively, that potentially cause adverse effect to biological molecules [14].

The mechanism of oxygen-dependent microbial killing is initiated after engulfment where oxygen burst is activated to cause increase in oxygen consumption (50- to 100-fold increase) and metabolism; this leads to massive production of nicotinamide adenosine diphosphate (NADP) as by-product of adenosine triphosphate (ATP) generation by oxidative phosphorylation. The oxygen burst is unrelated to mitochondrial respiration and reflects the activity of the NADPH oxidase system in the cytosol and membrane constituents, which are separated in resting microglia/phagocytes and are reassembled upon microglia/phagocytes activation. The generated NADP through NADPH oxidase enzyme activity generates superoxide (O_2^-) which is further converted to hydrogen peroxide (H_2O_2) either spontaneously or through enzymatic catalysis of superoxide dismutase (SOD) enzyme by combining with hydrogen ion (H^+). Both hydrogen peroxide (H_2O_2) and superoxide (O_2^-) can cause microbial killing. For instance, H_2O_2 in the presence of myeloperoxidase (MPO) released from microglia/phagocytes azurophilic (primary) granules and a halide generates very potent oxidizing agents such as hypochlorous acid (HOCl) and chloramines [13]. Other oxidative species such as singlet oxygen has been suggested to be important for microbial killing through the formation of ozone [15].

Non-oxygen-dependent/oxygen-independent microbial killing is mediated by protein molecule and other factors that are mostly found within the lysosome such as lysozyme, lactoferrin, and elastase. Lysozyme is an enzyme that hydrolyzes N-acetyl glucosamine bond found in glycopeptide coat of all bacterial cell wall. Thus, non-oxygen-dependent/oxygen-independent microbial killing is dependent on protein and peptide antibiotics such as bactericidal permeability-increasing protein, cationic antimicrobial protein 37, and defensins that are stored in peroxidase-positive (azurophilic, primary) granules where they are together localize with

active proteases such as elastase, cathepsin G, and proteinase 3. The synergistic interaction of oxygen-dependent and non-oxygen-dependent/oxygen-independent microbial killing systems generally results in pathogen killing [13].

Pathological consequences that result from a disease state of the brain, however, make microglia response becomes inappropriately exaggerated. Microglia when transformed into phagocytes can release a variety of substances many of which are cytotoxic and/or cytoprotective. While cytoprotective substances include neurotrophic molecules such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor I (IGF-I), several other growth factors, and anti-inflammatory factors, cytotoxic substances include proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 as well as other potential cytotoxic molecules including nitric oxide (NO), reactive oxygen species (ROS), and prostanoids. The uniquely outburst cytokines extensively studied in acute ischemic stroke are tumor necrosis factor-α (TNF-α); the interleukins (IL), IL-1β, IL-6, IL-20, and IL-10; and transforming growth factor (TGF)-β. Although IL-1β and TNF-α are proinflammatory that appears to exacerbate cerebral injury, TGF-β and IL-10 are anti-inflammatory that may exert neuroprotective effects, and IL-6 has both pro- and anti-inflammatory effects [16]. Astrocytes, like microglia, are also capable of secreting inflammatory factors such as cytokines, chemotaxis cytokines (chemokines), and NO in response to brain pathological state.

3. Agents that mediate neuroinflammation via TNF-α modulation

Table 1 reveals researches of various agents that mediate neuroinflammation via TNF modulation.

Treatment	Experimental model	Related TNF finding	References
Puerarin	Stroke model of rat middle cerebral artery occlusion	Modulate neuroinflammation by mark reduction in mRNA expression of tumor necrosis factor-α (TNF-α)	[17]
Edaravone and scutellarin	Stroke model of rat intraluminal middle cerebral artery occlusion	Modulate neuroinflammation by attenuating expression levels of TNF-α	[18]
Matrix metalloproteinase-8 inhibitor (M8I)	Stroke model of rat middle cerebral artery occlusion	Modulate neuroinflammation by abrogating TNF-α expression	[19]
Wogonin (5,7-dihydroxy-8-methoxyflavone)	Stroke model of rat middle cerebral artery occlusion	Modulate neuroinflammation by decrease in production of TNF-α	[20]
Nicotine	Stroke model of rat global cerebral ischemia	Modulate neuroinflammation by significant reduction of enhanced expression of tumor necrosis factor alpha (TNF-α)	[21]
Glycyrrhizin (GRZ)	Brain cognitive impairment and neuroinflammation of lipopolysaccharide treated Mice	Modulate neuroinflammation through inhibition of proinflammatory TNF-α	[8]
Atorvastatin	Stroke model of rat intracerebral hemorrhage	Modulate neuroinflammation by dose-dependent reduction of TNF-α	[22]
Angiotensin-(1–7)	Stroke model of mice intracerebral hemorrhage	Modulate neuroinflammation by decrease in levels of TNF-α	[23]

Treatment	Experimental model	Related TNF finding	References
Milk fat globule-EGF factor VIII (MFG-E8)	Stroke model of rat permanent middle cerebral artery occlusion	Modulate neuroinflammation through decrease in expression of cerebral TNF-α level	[24]
Compound K (20-O-D-glucopyranosyl-20 (S)-protopanaxadiol)	Stroke model of mice transient middle cerebral artery occlusion	Modulate neuroinflammation through inhibition of lipopolysaccharide-induced production of TNF-α	[25]
Kaempferol glycosides	Stroke model of rat transient middle cerebral artery occlusion	Modulate neuroinflammation by inhibiting expression of tumor necrosis factor alpha	[26]
Angiotensin-(1–7)	Stroke model of rat permanent middle cerebral artery occlusion	Modulate neuroinflammation by inhibiting increase in TNF-α	[27]
Nicotine	Stroke model of rat global ischemia	Modulate neuroinflammation by reduction of enhanced expression of tumor necrosis factor alpha (TNF-α) induced by ischemia/reperfusion	[21]
Propofol	Brain neuroinflammation of lipopolysaccharide-induced inflammation in activated microglia	Modulate neuroinflammation by inhibiting lipopolysaccharide-mediated production TNF-α	[28]
Zileuton	Stroke model of rat permanent middle cerebral artery occlusion	Modulate neuroinflammation through attenuating release of TNF-α in the serum	[29]
Caffeic acid ester fraction (Caf)	Stroke model of rat middle cerebral artery occlusion in vivo and lipopolysaccharide-induced microglial activation in vitro	Modulate neuroinflammation by inhibiting TNF-α induced by lipopolysaccharide treatment in primary microglia in a dose-dependent manner	[30]
Telmisartan	Stroke model of rat intracerebral hemorrhage	Modulate neuroinflammation by decrease in tumor necrosis factor-α	[31]
Setarud (IMOD™)	Human patients with acute ischemic stroke	Modulate neuroinflammation by decrease in TNF-α levels	[32]
Caffeine	Brain neuroinflammation of lipopolysaccharide (LPS)-stimulated murine BV2 microglial cells	Modulate neuroinflammation by suppressing generation of proinflammatory TNF-α	[33]
SCH58261	Stroke model of rat bilateral common carotid artery occlusion	Modulate neuroinflammation by reversing ischemia reperfusion injury induced elevation of TNF-α.	[34]
Caffeine	Stroke model of rat bilateral common carotid artery occlusion	Modulate neuroinflammation by reduction of TNF-α activity	[35]
Fluoxetine	Stroke model of rat subarachnoid hemorrhage	Modulate neuroinflammation by decreasing the expression of proinflammatory mRNA levels of TNF-α	[36]
Matrix metalloproteinases 8 (MMP-8) inhibitor	Brain neuroinflammation of lipoteichoic acid (LTA)-stimulated rat primary astrocytes	Modulate neuroinflammation by inhibiting lipoteichoic acid (LTA) induced expression of TNF-α	[37]
Sildenafil	Brain neuroinflammation and demyelination induced by cuprizone in Mice model of multiple sclerosis.	Modulate neuroinflammation by reduction in the expression of the proinflammatory cytokines TNF-α	[38]

Table 1
Various agents that mediate neuroinflammation via TNF modulation

4. Agents that induce neuroinflammation

In a comprehensive review of agents that induce neuroinflammation, Nazeem [39] has classified models of neuroinflammation based on mechanism through which agents induce neuroinflammation into three as follows: immune challenge-based models which include lipopolysaccharide (LPS)-induced neuroinflammation and polyriboinosinic-polyribocytidilic acid (PolyI:C)-induced neuroinflammation; neurotoxin-induced models which consist of streptozotocin-induced neuroinflammation, okadaic acid-induced neuroinflammation, and colchicine-induced neuroinflammation; genetically manipulated models that contain interleukin-1β (IL-1β) overexpression model, p25 transgenic model, anti-nerve growth factor (NGF) transgenic models, and transforming growth factor-β (TGF-β)-deficient models.

The most commonly studied model of neuroinflammation is LPS-induced neuroinflammation which activates microglia in the brain [40]. LPS also termed endotoxin is a constituent of the external membrane of Gram-negative bacteria, and the mechanism of LPS-induced neuroinflammation is mediated through LPS binding with CD14 on microglia membranes. The LPS-CD14 complex then interacts with the Toll-like receptor-4 (TLR-4), which, in turn, activates microglia by initiating signal transduction cascades leading to rapid transcription and release of proinflammatory cytokines, chemokines, and the complement system proteins, as well as anti-inflammatory cytokines like IL-10 and transforming growth factor-β (TGF-β) [39].

Another popular emerging noninvasive, effective, and sterile method of induction neuroinflammation in animal model is MRI-guided pulsed focused ultrasound (pFUS) combined with systemic infusion of contrast agent microbubbles (MB). This MRI-guided pFUS+MB has advantage over all other methods of inducing neuroinflammation in a way that it induces neuroinflammation without systemic involvement [40].

5. Mechanism leading to the production of TNF-α in the brain and TNF-α signaling

Within the brain, TNF-α is produced and discharged in the brain predominantly by glial cells and neurons, with microglia and astrocytes being the major glial cells involved. Upon arrival of appropriate TNF-α production stimulus, TNF-α is formed as a 27-kDa (233 amino acids) precursor, which binds to cell membrane of producing cells. This precursor is cleaved by proteolysis to liberate a 17-kDa (157 amino acids) subunit by the action of TNF alpha-converting enzyme (TACE). TACE also known as ADAM17 is well-identified proteinase enzyme that mediates the process TNF-α production and is a member in the family of mammalian adamalysins (or ADAMs: A disintegrins and metalloproteinases) [41].

Upon cleavage by TACE/ADAM17, the free TNF-α forms a bioactive homotrimer that lead to biological effect of TNF-α. The actions of TNF-α is achieved through two distinct cell surface receptors: TNFR1 and TNFR2. TNF-α generates the activation of TNF receptors (TNFR1 and TNFR2), and the resultant TNF-induced TNFR signaling pathways are complex and wide ranging in different cell types, and precise circumstances, thereby accounting for TNF-α pleiotropic nature of action [5]. For instance, with TNFR1 signaling pathway, binding of TNF-α to the cognate receptor leads to the recruitment of TNF-α adaptor protein termed as TNF receptor-associated death domain (TRADD), which then creates a platform

for binding of additional cytoplasmic adaptor proteins including TNF receptor-associated factor 2 (TRAF2), receptor-interacting protein (RIP), and FAS-associated death domain (FADD). The TRAF2 and RIP are concerned in escalating the transcriptional gene regulation; TRAF2 triggers the activation of a mitogen-activated protein kinase (MAPK) pathway, thereby leading to the activation of c-Jun N-terminal kinase (JNK), thus increasing its transcriptional activity; the RIP is a protein kinase vital to the activation of the transcription factor NFκB by phosphorylation of IκB kinase (IKK). On the other hand, FADD pathway leads to activation of caspase-8, thereby leading to initiate a caspase cascade of apoptosis cellular demise [41]. Although TNF-α binds to both TNFR1 and TNFR2 receptors with high affinity, there are some species specificity in terms of the receptor subtype and TNF-α binding [42]. TNF-α-induced p38 MAPK pathway transcription activity has been also implicated to induce proinflammatory IL-6 synthesis [43].

6. TNF-α and neuroinflammation

Neuroinflammation involves activation of microglia and astrocytes as well as influx of hematogenous cells recruited by cytokines, adhesion molecules, and chemokines across the activated blood vessel wall [44]. Neuroinflammatory signaling involves a coordinated effort of different molecules and cells types and is largely coordinated by a ubiquitous transcription factor NFκB. This signal transduction pathway for the activation of the transcription factor NFκB leads to control the expression of numerous genes activated during inflammation (i.e., cytokines, chemokines, growth factors, immune receptors, cellular ligands, and adhesion molecules). Thus, NFκB regulates a number of genes (including those coding for key inflammatory cytokines, like IL-6, TNF-α, etc.) involved in inflammation, making it the most important transcription factor that plays a key role in the inflammatory response. The collective gene targets of NFκB include various adhesion molecules, cytokines and chemokines (involved in proinflammatory signaling and NFκB activation, e.g., IL-1β and TNF-α), metalloproteinases (e.g., MMP-9), immune receptors, acute phase proteins, cell surface receptors, and inflammatory enzymes [45]. Various stimuli, such as cytokines, viruses, and oxidants, result in the activation of the transcription factor NFκB by separating it from inhibitor of NFκB alpha (IκBα)-bound protein in the cytoplasm, which becomes degraded and allows NFκB to move to the nucleus, where it binds to the DNA of the genes for numerous inflammatory mediators, resulting in their increased production and secretion [46].

It is pertinent to note that neuroinflammatory microglia-/macrophage-mediated phagocytosis is instrumental in neutralizing injurious foreign agent and conducting brain cleanup, the process which must occur to allow for tissue repair and functional recovery. This fast and efficient removal of apoptotic, dislocated, and damaged cells, before the discharge of injurious and proinflammatory cell contents occur, may help to reduce secondary damage. But inappropriate inflammatory responses generated by microglia/macrophages in a disease state may aggravate brain injury [45].

Proinflammatory TNF-α being one of the most key important early initiators of neuroinflammation interacts with two receptors R1 and R2, to mediate extrinsic apoptotic death signal via Fas-associated death domain (FADD) and inflammation via nuclear factor kappa-light-chain enhancer of activated B cells (NFκB), respectively [5]. NFκB is a major regulatory transcription factor with a pivotal role in inducing genes involved in inflammation [47]. In its dormant state, NFκB resides in the cytosol where it is bound to its inhibitory proteins known as inhibitors of NFκB (IκB), most commonly inhibitor of NFκB alpha (IκBα), making it unable to translocate into the nucleus [48]. Inflammatory stimuli resulting from wide range of

brain pathological processes, such as cerebral ischemia, leads to degradation of these inhibitors upon their phosphorylation by the IκB kinase (IKK), which allows NFκB to migrate into the nucleus, where it binds with DNA, and activates transcription of many proinflammatory genes [49]. This includes increase in expression of the genes for proinflammatory cytokines, chemokines, enzymes that generate mediators of inflammation, and adhesion molecules [50]. Thus, TNF-α both activate and are activated by NFκB, creating a type positive regulatory loop that amplify and perpetuate local inflammation [50]. Hence, these pathways of TNF-α-induced NF-kB explain the ability of TNF-α to induce other inflammatory cytokines such as IL-6 and IL-8 and synergize with interferons [5].

Apart from IκB-NFκB pathway, another intracellular signaling pathway through which TNF-α induces other inflammatory cytokines is Janus family of tyrosine kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. This JAK-STAT pathway can be initiated when there is TNF-α signaling after binding to its cognate receptors and consequently stimulates STATs. The STATs subsequently become activated and translocate to the nucleus to transmit transcriptional genetic expression of many cytokines, thereby leading to their synthesis [43].

Therefore, TNF-α is a proinflammatory cytokine that plays a critical role under both homeostatic and pathophysiological status within the central nervous system. Under healthy status, TNF-α has regulatory functions on vital physiological processes such as synaptic plasticity, learning and memory, sleep, food and water intake, and astrocyte-mediated synaptic amplification [51]. Under pathological status, astrocytes and mainly microglia excessively release massive concentration of TNF-α, thereby leading important constituent of neuroinflammatory response that marks a characteristic of several neurological disorders. Neuroinflammation itself at the first initial stage is a protective response in the brain, but excessively inappropriate inflammatory responses are detrimental, and in fact, it diminish the neuronal regeneration thereby leading to neurodegenerative diseases and other neurological disorders [52, 53].

7. Conclusion

Microglia is a pivotal brain endogenous protective mechanism against various injuries agents. If such an injury is tolerable, it triggers cellular responses that protect the brain and precondition the body against more severe stimuli. Beyond tolerable level, it triggers response that may potentially aggravate brain injury. TNF-α is released by microglia-induced NFκB activation, and activated NFκB in turn activates more TNF-α. The IκB-NFκB pathway together with other intracellular signaling pathway such as p38 MAPK pathway and JAK-STAT pathway that all orchestrate cascade of cytokine production makes TNF-α so-called master regulator of neuroinflammatory cytokine production. This phenomenon forms the basis of TNF-α as major cytokine of brain neuroinflammation.

Conflict of interest

The author declares no conflict of interest.

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