DOI: 10.53469/jcmp.2026.08(02).07

# The Role of Tumor Necrosis Factor-α in N740eurogenic Inflammation of Migraine

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**Abstract:** ***Migraine is a common chronic episodic brain dysfunction disorder with high prevalence and disability rates worldwide. It severely impacts patients' quality of life and imposes a heavy socioeconomic burden. Neurogenic inflammation plays a pivotal role in migraine pathogenesis, with tumor necrosis factor-α (TNF-α) serving as a key inflammatory mediator involved in the disease process. Traditional Chinese Medicine (TCM) offers unique insights into migraine pathogenesis through concepts like meridians and qi-blood dynamics. Additionally, certain active components in Chinese herbal medicines demonstrate effects on TNF-α and migraine. Future drug development targeting TNF-α and integrated treatment strategies hold promise for breakthroughs in migraine management. Research combining TCM and Western medicine will further expand therapeutic possibilities, thereby improving treatment outcomes and quality of life for migraine sufferers.***

**Keywords:** Migraine, Neurogenic Inflammation, Tumor Necrosis Factor-α, Traditional Chinese Medicine Theory, Therapeutic Outlook.

## 1. Introduction

Migraine is a common and complex neurovascular disorder whose high prevalence and disabling nature have drawn global attention. According to relevant data, migraine ranks second among all human diseases in terms of disability-adjusted life years lost, and it is the leading cause of disability-adjusted life years among women aged 15–49. It imposes significant negative impacts on patients, their families, and society [1]. Migraine primarily manifests as unilateral or bilateral throbbing headaches, often accompanied by nausea, vomiting, photophobia, and phonophobia. Severe cases may cause limb numbness or even paralysis. Due to its recurrent nature and difficulty in achieving complete cure, migraine profoundly impacts patients' quality of life, particularly in work, study, and social interactions. During attacks, patients often cannot engage in daily activities normally. Over time, this may lead to mental disorders such as depression and anxiety, further exacerbating the physical and psychological burden on patients. Furthermore, the chronic progression of migraine warrants attention. Approximately 3% of episodic migraine sufferers transition to chronic migraine annually, a phenomenon closely linked to medication overuse, inadequate treatment, and obesity [2]. Given migraine's substantial impact on patients and socioeconomic systems, in-depth research into its pathogenesis is urgently needed.

## 2. The Association Between Neurogenic Inflammation and Migraine

Neurogenic inflammation refers to an aseptic inflammatory response triggered by nervous system activation, characterized primarily by the release of inflammatory mediators and meningeal vasodilation mediated through the trigeminal vascular system [3]. In recent years, a growing body of research indicates that neurogenic inflammation plays a pivotal role in the pathogenesis of migraine. The mechanisms underlying migraine include the vascular theory, the cortical spreading depression (CSD) hypothesis, the neurotransmitter hypothesis, and the trigeminal vascular theory (TVS). Among these, the trigeminal vascular theory currently represents the mainstream explanation for migraine attacks. Related studies [4] suggest that activation of microglia in the caudal nucleus of the trigeminal nucleus (TNC) is a key factor in central sensitization. When relevant signals reach the TNC, neurons activate and release substances like adenosine triphosphate (ATP) and cyclic adenosine monophosphate (cAMP). These act on multiple receptors on the surface of microglia, prompting the release of inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). This sustained induction of TNC neuronal excitation leads to central sensitization [5]. When pain signals are transmitted to the trigeminal nucleus caudalis, headache symptoms are triggered. Throughout this process, multiple inflammatory mediators contribute to the formation and progression of neurogenic inflammation. Among these, TNF-α, as a key pro-inflammatory factor, is recognized as playing a pivotal role in migraine pathogenesis. Consequently, neurogenic inflammation not only represents a critical pathway in migraine development but also offers novel insights into understanding the pathophysiological mechanisms underlying migraine.

## 3. Biological Properties of TNF-α

Carswell et al. [6] first discovered that endotoxin itself does not directly kill tumors, but rather stimulates the host to release a serum factor, which they named TNF. Pennica et al. [7] identified TNF as a protein through subsequent research, subsequently determining its gene sequence and amino acid sequence, naming the macrophage-derived factor TNF-α. Further studies revealed TNF-α to be a multifunctional cytokine primarily secreted by immune cells, including macrophages, monocytes, neutrophils, and natural killer cells. Additionally, microglia and astrocytes within the central nervous system can synthesize and release TNF-α, with its levels significantly increasing under pathological conditions such as inflammation or infection [8]. Under normal

conditions, TNF-α plays a crucial role in immune regulation and inflammatory responses. As a key pro-inflammatory factor, TNF-α activates various immune cells, including T lymphocytes, B lymphocytes, and natural killer cells, thereby enhancing the body's immune defense capabilities [9]. Furthermore, TNF-α induces the release of other inflammatory mediators, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and interferon-γ (IFN-γ), forming a complex inflammatory cascade that amplifies the intensity of the immune response. Within these inflammatory responses, TNF-α promotes vascular endothelial cell activation, increases vascular permeability, and recruits additional inflammatory cells to the site of infection, thereby accelerating tissue repair processes. However, excessive or sustained TNF-α release may contribute to the onset and progression of chronic inflammatory diseases. Thus, TNF-α plays a dual role in maintaining immune homeostasis and the appropriateness of inflammatory responses, and its dysregulation is closely associated with the onset of various diseases [10].

## 4. The Role of TNF-α in Neurogenic Inflammation of Migraine

### 4.1 Participation in the Release of Inflammatory Mediators

TNF-α, as a key pro-inflammatory factor, regulates the release of other inflammatory mediators in migraine neurogenic inflammation. Related research [11] revealed that TNF-α activates vascular endothelial cells, mast cells, and mononuclear macrophages, thereby inducing the expression and secretion of inflammatory factors such as IL-6. This process not only exacerbates local inflammatory responses but also further promotes the transmission of inflammatory signals within the central nervous system. A study on chronic migraine (CM) [12] identified AMP-activated protein kinase (AMPK) as an intracellular energy sensor primarily derived from microglia. The M1 phenotype of microglia is associated with TNF-α release. TNF-α is considered a key inflammatory mediator driving neuroinflammation and central sensitization. Activating AMPK effectively reduces TNF-α levels by inhibiting the NF-κB pathway, thereby alleviating migraine symptoms including CGRP, IL-6, and IL-1β. Concurrently, TNF-α and IL-1β activate the trigeminal vasoactive system (TGVS), triggering CGRP and substance P release to induce persistent headaches [13]. Liang Xiaotao et al. [14] proposed that activated microglia are pivotal in initiating neuroinflammation and central sensitization. When the body experiences injury or stimulation, Toll-like receptor 4 (TLR4) is activated, subsequently initiating the downstream NF-κB signaling pathway. The activation of this pathway serves as the "master switch" for the release of inflammatory mediators, leading to the secretion of numerous pro-inflammatory cytokines (such as TNF-α, IL-1β, IL-6, and IFN-γ). These inflammatory mediators are key molecules responsible for neuroinflammation and central sensitization. Furthermore, nitric oxide (NO) upregulates TNF-α expression, while TNF-α further induces nitric oxide synthase (NOS) activity, amplifying inflammatory and vasodilatory effects [15]. Concurrently, NO-mediated oxidative stress directly activates the NF-κB pathway, further promoting the release of inflammatory cytokines [16]. Thus, the central role of TNF-α in inflammatory mediator release positions it as a key regulatory factor in the pathophysiology of migraine.

### 4.2 Direct Effects on Neurons

TNF-α not only participates in the release of inflammatory mediators but also modulates migraine pain signal transmission through direct effects on neuronal excitability and neurotransmitter release. Research indicates that TNF-α enhances neuronal excitability and disrupts the blood-brain barrier, allowing autoantibodies to enter the central nervous system. These antibodies bind to anti-N-methyl-D-aspartate receptors (Anti-NMDAR), causing neuronal damage [17]. Furthermore, by activating NMDA receptors, TNF-α promotes calcium influx, thereby altering neuronal membrane potential characteristics [18]. This action may lead to neuronal hyperexcitability, triggering the characteristic symptoms of migraine. Additionally, TNF-α modulates neurotransmitter release, particularly regulating the expression and secretion of calcitonin gene-related peptide (CGRP). As a key vasodilator in the trigeminal-vascular reflex theory, elevated CGRP levels cause meningeal and intracranial arterial dilation while promoting mast cell release of inflammatory mediators, thereby exacerbating neurogenic inflammatory responses [19]. Notably, the effects of TNF-α on neurons vary with concentration: low concentrations primarily exert neuroprotective effects, while high concentrations tend to induce neurotoxicity [20]. This dual mechanism indicates that TNF-α plays a complex and multifaceted role in migraine pain signaling, warranting further investigation.

### 4.3 Interaction with the Trigeminal Neurovascular System

The role of TNF-α in migraine neurogenic inflammation is further reflected in its close interaction with the trigeminal vascular system. The trigeminal vascular reflex theory posits that the primary pathological changes in migraine involve meningeal vasodilation and neurogenic inflammatory responses, with TNF-α playing a pivotal role in this process. CGRP, widely distributed throughout the trigeminal vascular system, serves as an initiator of neurogenic inflammatory pain [21]. The trigeminal neurovascular theory posits that relevant stimuli act on the trigeminal ganglion on the dura mater, thereby promoting the release of vasoactive substances such as CGRP. This leads to meningeal vasodilation and plasma protein extravasation, releasing inflammatory cytokines like IL-6 and TNF-α, resulting in pulsatile headaches [22,23]. This vasodilation not only increases vascular permeability but also facilitates the diffusion of inflammatory mediators, exacerbating the onset and progression of neurogenic inflammation. Chen Houdan et al. [24] demonstrated that the oxytocin (OXT)-ergic neuronal pathway from the paraventricular nucleus (PVN) of the hypothalamus to the GABAergic neurons in the trigeminal spinal caudate nucleus (TNC) exerts analgesic effects in chronic migraine. This pathway activates TNC GABAergic neurons via OXT–OXTR signaling, promoting GABA release to inhibit pain transmission. Ultimately, enhancing PVN OXT neuronal activity or TNC GABAergic inhibitory regulation may alleviate pain sensitization. Research by Liu et al. [25] demonstrated that high-frequency low-intensity

transcutaneous trigeminal nerve stimulation (HFLI eTNS) significantly alleviates pain hypersensitivity in chronic migraine. Its mechanism may involve inhibiting microglial activation, reducing expression of inflammatory mediators such as TNF-α, blocking neuroinflammatory signaling pathways, and promoting microglial polarization toward the M2 phenotype, thereby reversing central sensitization. Shi et al. [26] observed elevated TNF-α concentrations in trigeminal ganglia of nitroglycerin (NTG)-induced acute migraine mouse models. Following treatment with a programmed cell death ligand-1 (PD-1) inhibitor, TNF-α levels further increased alongside heightened pain sensitivity. suggesting the PD-1/PD-L1 pathway may alleviate migraine pain by suppressing inflammatory factors like TNF-α.

## 5. Traditional Chinese Medicine Theory on Migraine and Neurogenic Inflammation

### 5.1 Traditional Chinese Medicine's Interpretation of the Etiology and Pathogenesis of Migraine

Research on headaches in China dates back to ancient times. The earliest references appear in Shang Dynasty oracle bone inscriptions as "disease of the head" and "disease of the sky". The Yin-Yang Eleven Meridian Moxibustion Classic unearthed from the Mawangdui Han Tombs first explicitly termed it "headache." The Yellow Emperor's Inner Canon further classified headaches based on their etiology, pathogenesis, location, nature, and severity, assigning distinct names accordingly. The Suwen: Wind Theory states [27]: "Wind exposure after bathing causes head wind." "Wind energy ascending through wind passages causes brain wind." In traditional Chinese medicine, migraine is often classified as "one-sided head wind" or "head wind," with complex etiology and pathogenesis closely linked to visceral dysfunction and disrupted qi and blood circulation. According to meridian theory, the head is the convergence point of all yang meridians. All three yang meridians of the hands and feet traverse the head, while the foot jueyin liver meridian also ascends to the vertex. Thus, the liver meridian plays a crucial role in the development of migraine. Excessive Liver Yang is one of the most common pattern differentiation types for migraines. Literature analysis indicates that Liver Qi primarily ascends, being yin in substance yet yang in function. When Liver Yang becomes excessive, yin fails to restrain yang, leading to disordered qi and blood circulation. This ascends to disturb the clear orifices, thereby triggering migraines. Additionally, blood stasis obstructing the collaterals is another key pathogenesis of migraine. Emotional distress, invasion by external pathogens, or prolonged illness can impair qi and blood circulation, causing collaterals to stagnate. Obstruction leads to pain, further exacerbating migraine symptoms. From the perspective of qi and blood theory, both deficiency and dysfunction can result in inadequate nourishment of the brain orifices, thereby triggering migraine. Acupuncture at the Tai Chong (LR3) point, a classic treatment for calming liver yang and regulating qi and blood, has been proven to significantly improve clinical symptoms of liver-yang hyperactivity-type migraine, providing practical support for traditional Chinese medical theory [19].

### 5.2 Points of Convergence Between Traditional Chinese Medicine Theory and TNF-α

The concepts of qi and blood circulation and meridian unblocking in traditional Chinese medicine theory share certain parallels with the mechanisms of action of inflammatory mediators in modern biology. In TCM theory, qi and blood stasis is regarded as a fundamental pathological state underlying various diseases, exhibiting similarities to the inflammatory response in modern medicine. For instance, under conditions of qi and blood stasis, impaired local microcirculation may lead to tissue hypoxia and accumulation of metabolic byproducts, subsequently activating inflammatory response pathways—a process consistent with the TNF-α-induced inflammatory cascade [28,29]. Furthermore, TCM emphasizes that "unobstructed flow prevents pain, while pain indicates obstruction," viewing unimpeded meridian circulation as essential for maintaining health. CGRP amplifies inflammatory responses by regulating the production of inflammatory mediators like TNF-α, a process that can be interpreted as a manifestation of meridian obstruction [29]. Thus, from a TCM perspective, regulating qi and blood circulation and unblocking meridians may suppress excessive TNF-α expression, thereby alleviating migraine symptoms.

### 5.3 Effects of Active Components in Traditional Chinese Medicine on TNF-α and Migraine

Active components in traditional Chinese medicine demonstrate potential therapeutic value in regulating TNF-α expression and alleviating migraine symptoms. Gastrodin, one of the primary active constituents in Gastrodia elata, has been shown to possess significant neuroprotective effects. Research indicates [30] that gastrodin reduces neuronal damage, mitigates inflammatory responses following cerebral ischemia, and alleviates neurogenic inflammation by suppressing TNF-α expression. Xiong Hao et al. [31] discovered that multiple components in St. John's wort (e.g., hyperoside, hypericin, hyperforin) synergistically inhibit TNF-α-mediated inflammatory responses through cross-regulation of multiple signaling pathways (AMPK/p53/Nrf2, COX-2/5-LOX), thereby exerting anti-migraine effects. Yang Qingjie et al. [32] proposed that TNF-α, a cytokine with neurotransmitter effects, can disrupt neuroendocrine regulation when overexpressed. Tianma Headache Tablets, through their blood-nourishing, wind-dispelling, cold-dispersing, and pain-relieving effects, may suppress TNF-α-mediated neuroinflammatory responses. Group studies revealed that the herbal components in Tianma Headache Tablets effectively reduce elevated TNF-α levels in migraine patients. This regulation of inflammatory cytokines represents a key pathway for their clinical efficacy.

### 5.4 Effects of Acupuncture on Migraine

Zeng Yixiang et al. [33] found that the transient receptor potential vanilloid 1 (TRPV1) channel, acting as a nociceptor, mediates pain signaling and neurogenic inflammation when highly expressed. Activation of protein kinase C (PKC) phosphorylates TRPV1, lowering its threshold for mechanical and thermal stimuli and promoting pain sensitization. Electroacupuncture intervention significantly reduced the protein and mRNA expression of PKC, TRPV1, and its

phosphorylated form (p-TRPV1) in the trigeminal ganglion, thereby alleviating peripheral and central pain sensitization. Zheng Yuqi et al. [34] demonstrated that acupuncture intervention significantly elevated pain thresholds in rats on days 1, 3, 5, 7, and 9 post-treatment. This indicates acupuncture not only alleviates acute pain but also possesses sustained analgesic effects. Furthermore, acupuncture significantly reduced proinflammatory factors IL-1β and TNF-α in serum and trigeminal ganglion (TNC), while increasing the level of the anti-inflammatory factor TGF-β. This suggests that acupuncture alleviates peripheral and central inflammatory responses by suppressing neurogenic inflammation. Liu Jie et al. [35] demonstrated that the Liver-Soothing and Spirit-Regulating acupuncture technique significantly upregulates μ-opioid receptor (OPRM) expression in the anterior cingulate cortex, activating the endogenous analgesic system to inhibit migraine-related pain signaling. Concurrently, this technique downregulates serum levels of inflammatory factors IL-1β, IL-6, and TNF-α, thereby reducing neuroinflammatory responses and alleviating pain.

### 5.5 Modern Chinese Medicine Research on Migraine

Animal studies by Wang Kun et al. [36] demonstrated that San Pian Tang exhibits significant efficacy against neurogenic inflammation in migraine, primarily through blocking the p38 MAPK/iNOS pathway. This mechanism helps reduce the activity of pro-inflammatory factors such as NO, TNF-α, interferon-γ (IFN-γ), and interleukin-1β (IL-1β), thereby alleviating neuroinflammatory responses. Wang Yu [37] et al. studied 90 perimenopausal migraine patients and found that Xuefu Zhuyu Pills combined with repetitive transcranial magnetic stimulation (rTMS) was more effective than rTMS alone in reducing pro-inflammatory factor levels (IL-6, TNF-α, CGRP) and increasing anti-inflammatory factor levels (IL-10). Zeng Yunjuan et al. [38] evaluated the clinical efficacy of Pinggan Touhuang Tang in migraine patients (pattern of liver yang rising excessively). Sixty-four migraine patients were randomly divided into two groups of 32 each. The experimental group received Pinggan Touhuang Tang combined with flunarizine hydrochloride capsules, while the control group received flunarizine hydrochloride capsules alone. After 4 weeks of treatment, both groups showed reductions in headache score quantifications, traditional Chinese medicine syndrome scores, and HIT-6 headache impact scores compared to pre-treatment levels. Hao Tong et al. [10] observed the clinical efficacy of the Liver-Clearing and Depression-Resolving Optimized Formula in treating migraine patients and its effects on immune-inflammatory markers. Results indicated that the formula effectively alleviated headache symptoms in migraine patients, improved relevant symptoms in patients with Liver-Qi Stagnation with Heat Transformation syndrome, and reduced IL-6 and TNF-α levels compared to pre-treatment levels.

## 6. Summary and Outlook

In summary, TNF-α plays a crucial role in the neurogenic inflammation of migraine. As a core cytokine in migraine, TNF-α enhances neuronal excitability and interacts with the trigeminal-geniculate pathway (TGVS) by activating microglia and promoting the release of factors such as TNF-α, IL-6, and CGRP. This process facilitates central sensitization and the transmission of pain signals in migraine. Theories from Traditional Chinese Medicine (TCM) align with the mechanisms underlying TNF-α-mediated inflammatory responses. Relevant studies have demonstrated that active components in Chinese herbal medicines and acupuncture therapies can modulate related signaling pathways, suppress TNF-α expression, reduce inflammatory responses, and further alleviate migraine symptoms. Future development of TNF-α-specific antagonists may represent a novel therapeutic direction for migraine, while integrated Chinese and Western medicine treatment protocols hold significant promise. Additionally, exploring cross-talk between TNF-α and other inflammatory factors/neurotransmitters, along with the multi-target mechanisms of TCM in regulating inflammatory networks, will provide new insights for precision migraine treatment.

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