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Future Directions of Cytokine Hypothesis in Depression: 'NLRP3 Inflammasome'

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ÖZET:

Depresyon ve sitokin hipotezinde yeni ufuklar: 'NLRP3 inflamazomu'

Depresyon prevalansının tip II diyabet, kardiyovasküler hastalıklar, otoimmün kaynaklı romatoid artrit, sistemik lupus eritamatozus gibi kronik inflamatuvar hastalıklar eşliğinde arttığı bilinmektedir.

Geçtiğimiz on yıllık süreç içerisinde periferde oluşan inflamatuvar yanıtların santral sinir sistemini etkileyebileceği gösterilmiştir. İnflamatuvar bir uyaran beyine ulaştığında, mikroglia hücreleri sensör görevi görerek nöroinflamasyon sürecinin başlatırlar. Nöroinflamasyon normal şartlarda beynin gelişimi için gerekli bir süreç olmasına karşın kronik stres ya da depresyon tablosunda olduğu gibi uzun süreli veya şiddetli bir tetikleyici inflamatuvar faktör varlığında patolojik bir tabloya dönüşerek hastalık etkeni haline gelebilmektedir.

Günümüzde klinik ve deneysel çok sayıda çalışma depresyon tablosu ile artmış proinflamatuvar sitokin seviyeleri arasındaki ilişkiye dikkat çekmektedir. Mevcut antidepresan tedaviler ile depresyon hastalarında yüksek seyreden söz konusu sitokin seviyelerinin azaldığı ve sitokin aracılı immün yanıtları baskılayan ajanlarla antidepresan benzeri etkiler elde edildiği gösterilmiştir. Diğer taraftan inflamatuvar sitokinlerin depresyon hastalarında arttığı bilinen hipotalamus-hipofiz-adrenal (HPA) ekseninin aktivasyonunda rol oynayarak inflamasyon tablosunun daha da güçlenmesine yol açtıkları düşünülmektedir.

Depresyon hastalarının yaklaşık %30'unun mevcut antidepresan tedavilere yanıt vermediğinin bilinmesi, günümüzde depresyonda yeni mekanizmal hedefler ve tedavi yaklaşımlarına yönelik çalışmaları beraberinde getirmektedir. Bu noktada sitokin-aracılı inflamatuvar yanıtları başlatan moleküler mekanizmaların araştırılması, sürece sitokinlerin üretim ve salınım aşamalarının öncesinde müdahale getirilebilmesi yönünden ilgi çekici bir konu niteliği taşımaktadır. Bu gözden geçirme çalışmasında, depresyonda sitokin hipotezine yeni bir bakış açısı kazandırabilmesi ve olası yeni tedavi hedeflerini gündeme getirebilmesi bakımından; IL-1β ve IL-18 aracılı inflamatuvar yanıtların başlamasında görev alan; makrofaj ve mikroglia hücrelerinde oluşum gösteren multiprotein kompleks yapısındaki NLRP3 inflamazomu ve ilişkili yolakların ele alınması amaçlanmıştır.

Anahtar sözcükler: İnflamazom, depresyon, sitokin, proinflamatuvar, IL-1β, mikroglia, NLRP3

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ABSTRACT:

Future directions of cytokine hypothesis in depression: 'NLRP3 inflammasome'

The prevalence of depression has been shown to be increased with the presence of chronic inflammatory and/or autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, type II diabetes mellitus and cardiovascular diseases.

It has been well documented in the last decade that inflammation in the periphery could interact within the central nervous system. Once an inflammatory stimulus reaches the brain, microglial cells serve as fundamental sensory complements by playing an important role in neuroinflammation which is a necessary process required for brain development. However, the process itself, if excessive or prolonged, can turn into a pathological condition and become a causative factor of the disease, for example, in the case of chronic stress or depression.

The association between high plasma levels of proinflammatory cytokines and depression has been shown by several clinical and experimental studies. In addition, current antidepressant therapies reduce high cytokine levels of depressive patients and antidepressant-like effects are observed with the use of immunosuppressant drugs acting on cytokine-mediated mechanisms. On the other hand, inflammatory cytokines are known to mediate the activity of the hypothalamic-pituitary axis (HPA) which is well known to be elevated in depression and stress, resulting in a further contribution to the inflammatory state. At present, approximately 30% of patients with depression do not respond to current antidepressant therapies. Thus, great efforts have been made in many studies to provide novel therapeutic approaches for depression. At this point, targeting initiator molecular mechanisms of cytokine-mediated inflammatory responses has become an intriguing approach for preventing the process before the production and release of these inflammatory mediators. Herein, we have aimed to draw attention to a novel aspect of the cytokine hypothesis of depression that may serve as a novel target mechanism and provide further understanding of the disease, namely NLRP3 inflammasome, a multiprotein complex formed in macrophage and microglia cells which is responsible for initiating the inflammatory responses mediated with IL-1β and IL-18.

Key words: Inflammasome, depression, cytokine, proinflammatory, IL-1β, microglia, NLRP3

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INTRODUCTION

Major depression, a progressive psychiatric disorder characterized by depressed mood, anhedonia, low self-esteem and a feeling of worthless which is usually accompanied with disturbances of sleep, eating and cognitive functions, can cause death related thoughts ending up with suicidal events in the lack of adequate treatment. By 2020, following ischemic heart disease, major depression is estimated to be the second line worldwide disease in terms of bringing social and economic burden to society (1,2).

The monoamine hypothesis has been accepted to define the pathophysiology of depression for more than half a decade (3,4). However, it is now well established that approximately 30% of patients with major depression do not respond to the current pharmacological treatments that exert their effects by enhancing serotonergic neurotransmission (5-7). In light of this knowledge, even though the decrease in monoamine substances in the brain is well established in depression, the monoamine hypothesis alone is not adequate for comprehensively understanding the pathogenesis of the disease (4,7). At present, great efforts have been made by many studies to further the understanding of the pathogenesis of depression and search for novel targets, of which perhaps one of the most promising is the involvement of immune mechanisms in depression, ie. the cytokine hypothesis. In this critical review, we have aimed to draw attention to a particular initiator mechanism of cytokine-mediated inflammatory responses, NLRP3 inflammasome, which may contribute to novel therapeutic approaches to depression.

Depression and the Cytokine Hypothesis

The prevalence of depression has been shown to be increased with the presence of chronic inflammatory and/or autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, type II diabetes mellitus and cardiovascular diseases. While in the general population, the prevalence is about 10.3%, with type II diabetes mellitus and rheumatoid arthritis, it increases up to 26% and 13-20%, respectively (2,8).

High plasma levels of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α have been reported by several clinical studies in patients with depression (9-11). In addition, with antidepressant therapies such as tricyclic antidepressants (TCAs) and serotonin re-uptake inhibitors (SSRIs), plasma levels of these pro-inflammatory cytokines are shown to be decreased (12). According to a recent meta-analysis, in contrast to the decrease in IL-1β levels, no significant changes in TNF-α levels were observed with antidepressant therapy, indicating that IL-1β might play a specific role in response to the treatment and also might serve as a biomarker in the diagnosis of depression (11). On the other hand, etanercept, a soluble TNF-α receptor that binds to TNF-α and inhibits its activity, has been shown to reduce depressive symptoms when used in patients with psoriasis (13).

It has been well documented in the last decade that inflammation in the periphery can interact within the central nervous system (6,14,15). When cytokines, especially TNF-α and IL-1β, are peripherally induced they can enter the brain through several mechanisms such as passing through circumventricular organs (16), uptake by active transport systems (17-19), projection with peripheral vagal nerve afferents (20), crossing of cytokine induced immune cells such as monocytes, macrophages, T cells from the blood brain barrier (21) and direct passage (19). After accessing the brain, these cytokines induce their own synthesis (22) especially in the hypothalamus, dentate gyrus of the hippocampus, amygdala and other brain regions (23,24).

Microglia cells which under normal conditions remain as silent bodies responsible for maintaining the healthy environment and helping the development of the brain by providing trophic support to neurons, serve as fundamental sensory complements of the brain for both initiating and responding to the inflammatory stimuli which under normal conditions (25). Once they are activated by an inflammatory state reaching the

brain, they can migrate to clear damaged cells and also produce inflammatory cytokines. Thus they play an important role in neuroinflammation which is a required process helping the resolution of inflammation and repairing the damaged area (26). However, the process itself, if excessive or prolonged, can turn into a pathological condition and become as a causal factor of the disease. In the presence of prolonged stress, microglia mediated pro-inflammatory responses are known to be induced (27). In addition, microglia activation induced by lipopolysaccharide (LPS) or interferon gamma (IFN-γ), is inhibited by SSRIs and ketamine, a NMDA channel blocker, and this effect is also accompanied with reduced levels of TNF-α and nitric oxide (28-30).

It has been stated that approximately 73% of patients with depression have higher plasma cortisol levels than healthy individuals (31). Inflammatory cytokines are considered to mediate the activity of hypothalamic-pituitary axis (HPA) which is well known to be increased in the presence of depression and stress. IL-1β has been shown to activate corticotrophin releasing hormone (CRH) release from the hypothalamus, resulting in an increased release of adrenocorticotrophic hormone (ACTH) from the pituitary and finally steroidogenesis in adrenal glands (32). This effect is postulated to be supported by the reduction of glucocorticoid receptor functions and their expressions, resulted in disruption of negative feedback to the HPA (33,34). The correlation between plasma IL-1β levels and glucocorticoid resistance seen in depressive patients strongly supports the idea of the contribution of pro-inflammatory cytokines to HPA in depression (34). Additionally, high plasma glucocorticoid levels are related to atrophy of pyramidal cells in the hippocampus and medial prefrontal cortex accompanied by reduced levels of brain derived neurotrophic factor (BDNF) and induction of depressive symptoms (2,35,36).

In experimental studies, administration of pro-inflammatory cytokines to subjects has been shown to cause depressive like behaviors. Behavioral alterations, such as reduction in locomotor activity, social exploration and feeding behavior, anhedonia, anxiety like behaviors and disruption in learning and memory, have been observed after administration of IL-1β. Similarly, systemic administration of TNF-α reduced social exploration and induces weight loss, while central administration resulted in helplessness behavior and inhibition of social interaction in addition to weight loss. Administration of an IL-1 receptor antagonist has been shown to prevent those behavioral alterations developed by TNF-α, leading to the conclusion that endogenous IL-1 can mediate the changes seen with TNF-α (2,37-40).

In addition to the interrelated mechanisms between pro-inflammatory cytokines and the HPA, induced activation of the indoleamine pathway by cytokines resulted in excessive glutamatergic neurotransmission, a major concern that is highly involved with the development of depression. However, since this review is intended to outline the initiator mechanisms of cytokine-mediated inflammatory responses, we will refer the reader to studies related to this subject (41-47).

NLRP3 Inflammasome and Depression

With the establishment of the cytokine hypothesis of depression, the initiator mechanisms of cytokine-mediated immune responses have become intriguing subjects. NLRP3 inflammasome, a multiprotein complex that is formed by the activation of Nod-like receptor protein 3 (NLRP3) and is responsible for initiating IL-1β and IL-18-mediated inflammatory responses (48-51), has become an important topic which may add novel aspects to the cytokine hypothesis of depression. There are several promising findings which contribute to this possibility such as: acute restraint stress has been shown to induce NLRP3 activation of the hippocampus in experimental animals (2); significantly reduced expression and activation of IL-1β has been demonstrated in NLRP3-null mice (52) and high levels of IL-1β seen in stress and depression have been reduced by gliburide, an antidiabetic agent used in the treatment of type II diabetes, which also serves as a NLRP3 antagonist (53).

NLRP3 Inflammasome: Initiating IL-1β and IL-18- Mediated Immune Responses

NLRP3, a member of the NLR family which also includes NLRP1, NLRC4, AIM2, is a cytosolic receptor protein that was characterized for the first time in the early 2000s as a cytoplasmic caspase-1 activating self-oligomerization signaling complex, especially located in immune system cells such as macrophages and microglia, responsible for recognizing danger signals and initiating IL-1β and IL-18 mediated inflammatory responses. NLRP3 is set apart from other NLR members by its characteristic for recognizing a wide range of danger signals (54,55). To activate inflammasome, macrophage or microglia cells are required to encounter danger signals which can be referred to as pathogen-associated molecular patterns (PAMPs) or damage- associated molecular patterns (DAMPs). After the recognition of these signals by Toll like receptors (TLRs) located on the microglia/ macrophage cell membrane, pro-inflammatory cytokines, such as IL-6 and TNF-α, are directly released by induction of their gene transcriptions, while a separate second base mechanism is required for the release of IL-1β and IL-18, which is developed in a result of inflammasome activation. Stimulation of TLRs triggers the downstream signaling cascades resulting in maturation of MAPKs and activation of NF-κB which later results in production of pro-IL-1β and pro-IL-18, progenitor forms of these two cytokines, in addition to induction of NLRP3 gene transcription through the NF-χB pathway. For a second base, activation of NLRP3 inflammasome and transformation of pro-caspase-1 to caspase-1 are both required for these two pro-cytokines to be transformed into their mature forms and finally released. At this point, caspase-1 is responsible for transforming these two pro-cytokines into their mature forms. On the other side, activation of P2X7 receptors, an ATP-mediated cation channel coupled receptor, and consequently K^+ ion efflux from the cell are required for oligomerization of NLRP3 to finally form the inflammasome complex. P2X7 receptors are coupled with large membrane pores known as the pannexin-1 channel, which allows the passage of large molecules from the cell membrane. It has been shown that the production of IL-1β by P2X7 receptor activation is inhibited when the pannexin-1 channel is blocked. NLRP3 structurally consists of three compartments which include C-terminal leucine rich repeat domain (LRR), centrally localized nucleotide binding oligomerization domain (NACHT) and N-terminal pyrin domain (PYD). ASC protein and pro-caspase-1 binds to NLRP3 to form the inflammasome complex after its activation through P2X7 receptors resulting in caspase-1 activation. At this binding phase, ASC protein forms as a bridge between NLRP3 and caspase-1 with its pyrin and CARD domains that bind the N-terminal PYD of NLRP3 and the CARD domain of pro-caspase-1, respectively. This binding consequently develops caspase-1 from pro-caspase-1, thus producing the active forms of pro-IL-1β and pro-IL-18, IL-1β and IL-18 (2,54-59) (Figure 1). Activation of caspase-1 further induces pyropitosis mediated cell death (59).

Modulatory Mechanisms of NLRP3 Inflammasome Activation

Activation of NLRP3 inflammasome is regulated primarily by a number of intracellular events such as autophagy, mitochondrial reactive oxygen species, miRNA223, and P2X7 receptors (59-66).

Autophagy and cytokines are known to have a bidirectional modulatory mechanism with each other. Autophagy has been shown to be induced by TNF-α, IFN-γ, IL-1, IL-2 and IL-6, and inhibited by IL-10, IL-4 and IL-13. On the other hand, autophagy itself regulates the production of cytokines such as IL-1, IL-18 and TNF-α (60). It has been shown that autophagy inhibition in macrophage and dendritic cells pharmaceutically with 3-methyladenine (3-MA) or in the lack of autophagy gene, increases IL-1β and IL-18 levels in response to TLR agonists (61). Saitoh et al. have stated in their study that the production of IL-1β and IL-18, in response to the stimulation of TLRs with LPS, was higher in the Atg16L1 protein deficient mice compared to the control group (62). In another study, increased levels of IL-1β by autophagy inhibition with 3-MA

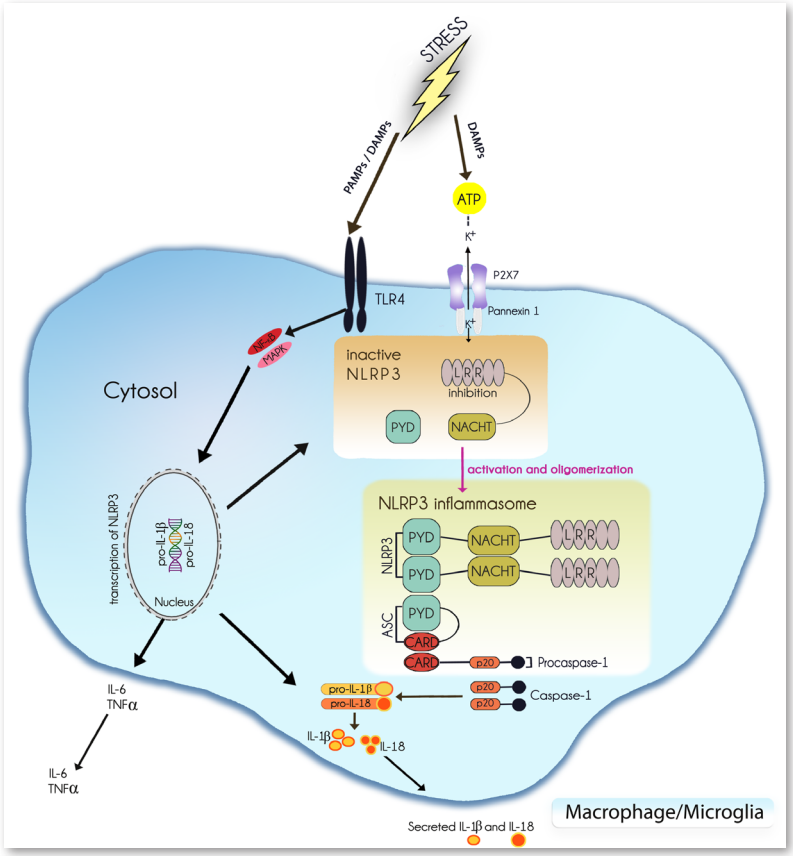

Figure 1: Activation of NLRP3 inflammasome and production of IL-1β and IL-18
NLRP3, a member of NLR family, is a cytosolic receptor protein especially located in immune system cells such as macrophages/microglia and is responsible for recognizing danger signals resulting in the formation of the inflammasome complex, which initiates IL-1β and IL-18 mediated inflammatory responses. For inflammasome formation, macrophage/microglia cells are firstly required to recognize danger signals by TLRs. Stimulation of TLRs by PAMPs or DAMPs, such as in the case of exposure to stress, triggers the downstream signaling cascades resulting in maturation of MAPKs and activation of NF-κB. Consequently, gene transcriptions of IL-6, TNF-α, pro-IL-1β, pro-IL-18 and NLRP3 are induced in the cell nucleus. While IL-6 and TNF-α are directly released from the cell membrane after this production phase, a separate second base mechanism is required for secretion of the mature forms of IL-1β and IL-18, which is the activation of NLRP3 and formation of the inflammasome complex. At this point, stimulation of cation channel-coupled P2X7 receptors with ATP, causes K^+ ion efflux from the cell membrane and results in oligomerization of NLRP3 to form an inflammasome complex. This stimulation relieves the autoinhibition of NLRP3 which is the binding of the LRR domain to the NACHT domain (inactive form), therefore enabling NLRP3 oligomerization and binding with pro-caspase-1 through the adaptor protein ASC. This binding phase consequently develops caspase-1 from pro-caspase-1, thus produces active forms of pro-IL-1β and pro-IL-18; IL-1β and IL-18. (PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; TLR4, Toll like receptor-4; NF-κB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; LRR, leucin rich repeat domain; NACHT, nucleotide binding oligomerization domain; PYD, pyrin domain; NLRP3, nod-like receptor protein 3; ASC, apoptosis-associated speck-like protein containing CARD.)

was shown to be decreased when the production of reactive oxygen species (ROS) was inhibited (63). Additionally, the induction of autophagy both with in vitro and in vivo by rapamycin administration decreased the production of IL-1β and its serum levels in response to TLR stimulation according to the same study (63). This effect of autophagy on IL-1β and IL-18 production is considered to be dependent on TIR-domain-containing adapter-inducing interferon-β (TRIF) and mitochondrial ROS/DNA (61,64).

Two ROS-related NLRP3 ligands have been defined, oxide DNA that is released to cytosol by mitochondrial dysfunction and thioredoxin interacting protein (TXNIP), which are thought to be responsible for the activation of NLRP3 inflammasome (59). Zhou et al. showed that mitochondrial ROS caused NLRP3 inflammasome

activation, which could be reversed by the induction of autophagy (66).

Within the recent discovery that miRNA-mediated post-transcriptional regulations are important for controlling gene expressions as well as the transcription phase, it has been suggested that miRNA might play a role in regulating the activation of NLRP3 inflammasome. It has been shown that the over expression of miRNA223, that is specific for myeloid cells, is accompanied by reduced production of IL-1β in response to NLRP3 activators such as ATP and nigericin in LPS stimulated macrophage cells of mice (67), suggesting that miRNA223 may be responsible for negative regulation of NLRP3 inflammasome (59,67).

As mentioned in the previous section, stimulation of ATP-mediated P2X7 receptors is required for NLRP3 to be activated. P2X7 receptors, members of purinergic receptor family, belonging to the P2 subtype that is mediated by ATP and its related metabolites, are the seventh type of P2X receptors that are non-specific cation channel coupled ionotrophic receptors. Unlike other members, P2X7 receptors, located on macrophage and monocyte cells, are associated with inflammatory processes by having a role in production of IL-1β and IL-18. There are numerous studies outlining the contribution of P2X7 receptors to various inflammatory conditions such as renal, rheumatologic and neurological diseases, sepsis and so on. In addition, P2X7 receptors have been shown to be up-regulated around amyloid plaques in Alzheimer's disease. In a neuropathic pain model, increased responses to mechanical stimuli (allodynia and hyperalgesia) have been shown to be reduced in P2X7 receptor knock-out mice and this effect was accompanied by decreased levels of IL-1β, IL-6 and TNF-α (68).

In very recent studies, antidepressant-like effects have been observed in P2X7 receptor knock-out mice and according to a non-published study by Iwata et al., administration of P2X7 receptor antagonist reduced the depression state in the chronic unpredictable mild stress model (2). Similarly, systemic administration of a non-selective P2X receptor antagonist reduced immobility time in the forced swim test in mice (69).

CONCLUSION

At present, growing evidence strongly suggests the link between elevated inflammatory cytokines and depression. Great effort has been made to discover novel therapeutic implications targeting immune mechanisms that would equal the current available antidepressant therapies acting on monoaminergic neurotransmission in terms of efficiency and safety. Inhibition of both centrally and peripherally induced cytokines, especially IL-1β, TNF-α, IL-6, is of main target. However, since the available inhibitors of these cytokine receptors consist of large molecules and are restricted to biological antibodies, this approach is accepted as conceptual at this moment. Hence, targeting initiator molecular mechanisms of cytokine-mediated inflammatory responses has become an intriguing subject for preventing the inflammatory event before the production and release processes. In this context, NLRP3 inflammasome and its regulatory mechanisms may represent novel potential targets and possibly provide further advances in the treatment of depression.

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