The Potential Negative Effects of Interleukin-1β in Multiple Sclerosis Patients with MEFV Mutation

MEFV Gen Mutasyonlu Multipl Skleroz Hastalarında İnterlökin-1β'nın Potansiyel Olumsuz Etkileri

Multipl Sklerozda İnterlökin-1β / Interleukin-1β in Multiple Sclerosis

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Özet

MEditerranean FeVer (MEFV) gen mutasyonlu multipl skleroz hastaları, bu mutasyonu taşımayanlara kıyasla daha hızlı ilerleyen hastalığa sahiptirler. Ancak, bunun mekanizması henüz tam olarak aydınlatılamamıştır. Bu yazı, bu hızlı ilerlemeden sorumlu olabilen interlökin-1β (IL-1β)'nın muhtemel rolünü önermektedir. MEFV geni, pyrin proteinini kodlar ve mutasyonları ailesel Akdeniz ateşine neden olur. MEFV mutasyonları, pyrin fonksiyonunun ortaya çıkmasına yol açar ve IL-1β'nın uygun olmayan salınımıyla sonuçlanır. İnterlökin-1β, sistemik inflamasyon ve ateşin majör bir medyatörüdür ve aynı zamanda multipl sklerozun aktif lezyonlarında kan-beyin bariyerinin geçirgenliğine katkıda bulunur. Dahası, IL-1β nöronların ve aksonlara yalıtım sağlayan miyelin kılıfı üreten oligodendrositlerin apoptozisini teşvik eder. Böylece, multipl sklerozun patogenezinde ve klinik seyrinde önemli rol oynayan inflamatuar hasar, kan-beyin bariyeri disfonksiyonu, ateşin santral sinir sistemi üzerine etkileri (veya Uhthoff fenomeni) ve nöronların ve oligodendrositlerin apoptozisi MEFV gen mutasyonlarının varlığında IL-1β'nın artmış aktivasyonu ve salınımı aracılığıyla indüklenmiş olabilir. Bu nedenle, multipl skleroz hastalarında MEFV mutasyonlarını taramak ve taşıyıcılar için IL-1β'yı hedefleyen ilaçlarla tedavi planlamak, bilimsel çalışmalar için ilham kaynağı olacak mantıklı bir fikir olabilir.

Anahtar Kelimeler

Multipl Skleroz; MEFV; İnterlökin-1β; Akdeniz Ateşi

Abstract

Multiple sclerosis patients, who are carriers of MEditerranean FeVer (MEFV) gene mutation, have faster progression than the non-carriers. However, its underlying mechanism is not well understood. This article proposes the potential role of interleukin-1β (IL-1β) that may be responsible for this rapid progression. Mutations in MEFV, the gene encoding for protein pyrin, cause familial Mediterranean fever, lead to gain of pyrin function, resulting in inappropriate IL-1β release. Interleukin-1β is a major mediator of systemic inflammation and fever, and also it contributes to permeability of the blood-brain barrier in active lesions of multiple sclerosis. Moreover, IL-1β promotes apoptosis of neurons and oligodendrocytes that produce the myelin sheath, which insulates axons. Thus, inflammatory damage, the blood-brain barrier disfunction, effects of fever on the central nervous system (or Uhthoff's phenomenon), and apoptosis of neurons and oligodendrocytes, which play an important role in the pathogenesis and clinical course of multiple sclerosis, can be induced by increased activation and release of IL-1β in the presence of MEFV gene mutations. Therefore, screening for MEFV mutations in patients with multiple sclerosis and treatment planning with IL-1β targeting drugs for the carriers, may be a logical idea that will be a source of inspiration for scientific studies.

Keywords

Multiple Sclerosis; MEFV; Interleukin-1β; Mediterranean Fever

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Introduction

MEditerranean FeVer (MEFV) gene locates on chromosome 16 and encodes a protein called pyrin [1,2]. Mutations of the MEFV gene result in increased synthesis of pyrin [3] and cause familial Mediterranean fever (FMF) that is the prototype of autoinflammatory syndromes [4]. Pyrin is a significant intracellular regulator of apoptosis, inflammation, and cytokine processing. It appears to be a major regulator of inflammation and innate immunity in patients with FMF [3], and a mutated pyrin probably results in uncontrolled inflammation [5]. Experimental studies [6,7] have demonstrated that MEFV gene mutations can lead to gain of pyrin function, resulting in inappropriate interleukin-1β (IL-1β) release [6], and pyrin mutations induce IL-1β activation and severe autoinflammation in mice [7]. Also, it has been found that mononuclear cells from FMF patients release higher levels of IL-1β [8]. IL-1β is a major cytokine of systemic inflammation and fever [9,10]. It increases the expression of other cytokines, such as tumor necrosis factor (TNF)-α and IL-6, and the chemokines as well as adhesion molecules [10]. Moreover, IL-1 plays an important role in the regulation of T-cells' activation, and it is considered an essential cytokine for T helper (Th) cell differentiation [11].

Multiple sclerosis (MS) is a chronic and progressive inflammatory disorder of the central nervous system (CNS) that is generally considered to be autoimmune and characterized by widespread lesions, plaques and demyelination in the brain and spinal cord [12]. Multiple sclerosis lesions show a great heterogeneity in terms of structural and immunopathologic characteristics. This varies depending on the phase of the demyelinating activity. Whereas active lesions show dense macrophage infiltration, chronic inactive lesions are poor in cells. In chronic lesions, number of mature oligodendrocytes and axon density have prominently decreased, and remyelination is not complete [13,14].

Increased evidences indicate a strong genetic contribution to MS susceptibility, although others support the view that it is also influenced by environmental factors, such as virus infections, geographical distribution, smoking, hypovitaminosis D and exposure to sunlight [15,16]. Recent genetic studies confirmed that immunologically relevant genes within the major histocompatibility complex are especially implicate Th cell differentiation in the pathogenesis of MS [17].

Although the actual cause of MS is not known exactly, inflammation of the CNS is the primary reason of damage in this disease [18]. The specific factors that start this inflammation are still unknown. Approximately 87% of patients present with relapsing remitting MS (RRMS), characterized by acute attacks (relapses) followed by partial or full recovery (remission) [18]. Relapses result from acute focal inflammation of the CNS. The acute focal lesion is characterized by an inflammmatory central region and indistinct margin [14]. Increased proinflammatory cytokin IL-1β levels have been detected in MS lesions, and elevated IL-1β cerebrospinal fluid and serum lev¬els have also been reported in patients with RRMS in comparison to healthy controls [11].

To date there is no cure for MS, but treatment with IL-1 targeting drugs such as IFNβ and glatiramer acetate display beneficial effect by reducing the disease severity. Interleukin-1β activity is inhibited by the secreted form of IL-1 receptor antagonist whose production is increased in patients' blood and induced in human monocytes by IFNβ and glatiramer acetate [19].

Discussion

Recent studies have found that MS patients, who are carriers of MEFV gene mutation, have faster progression than the non-carriers [20,21]. However, its mechanism has not been enlightened in full yet. This article proposes the potential role of IL-1β that may be responsible for this rapid progression.

MEFV gene mutations lead to gain of pyrin function, resulting in inappropriate IL-1β release [6], and pyrin mutations induce IL-1β activation and severe autoinflammation in mice [7]. Also, mononuclear cells from FMF patients release higher levels of IL-1β [8]. Moreover, a recent study by Yildirim et al. [22] confirmed the presence of increased IL-1β levels in FMF patients during attack-free period.

It has been shown that innate production of IL-1β is a risk factor for susceptibility and progression of relapse-onset MS [23]. Interleukin-1β is a major mediator of systemic inflammation [9,10], and inflammation of the CNS is the primary cause of damage in MS [18]. Interleukin-1β increases the expression of other proinflammatory cytokines, such as TNF-α and IL-6 [10]. Therefore, expressed MEFV mutations in MS patients can increase the inflammatory damage by proinflammatory cytokin IL-1β.

Moreover, IL-1β promotes apoptosis of neurons and oligodendrocytes, thereby contributing to the inflammation-mediated damage of the CNS parenchyma [11,24]. Researchers who investigated the active lesions of MS have described four different immunopathologic types [25,26]. These are demyelination associated with macrophages, demyelination related to antibody/complement, oligodendrogliopathy concurrent with apoptosis, and primary oligodendrocyte degeneration. Accordingly, while the 1st and 2nd types target the myelin, and the 3rd and 4th types target the oligodendrocytes. The oligodendrocytes of the CNS and the Schwann cells of the peripheral nervous system (PNS) are best known for making the myelin that sheaths and insulates neuronal axons [27]. The induction of apoptosis of neurons and oligodendrocytes due to increased IL-1β levels may delay and prevent the re-myelination of demyelinated axons. Thus, inflammation and demyelination, when combined by the effects of IL-1β, might increase the axonal damage and affect the prognosis of MS, because axonal degeneration causes irreversible neurological damage in MS [28].

In the existence of MEFV mutations, another factor causing rapid progression in MS may be BBB disfunction by IL-1β, because IL-1β contributes to permeability of the BBB in active MS lesions [11,29]. Owing to the function of BBB that is an endothelial barrier, CNS parencyma is immunologically protected. However, endothelial dysfunction, vascular damage and vasculitis, which occur in the existence of MEFV gene mutation [30,31], may cause the BBB deterioration that is an early and prominent event in the development of MS lesions [29]. Some studies [30] showing elevation of circulating markers of endothelial dysfunction and vascular damage such as thrombomodulin, adrenomedullin, nitrite, and acute-phase reactants during symptom-free intervals of FMF support this view. Furthermore, IL-1β is detected in active MS lesion in the microglia, astrocytes and in brain endothelial cells, where it contributes to BBB permeability via induction of the vascular endothelial growth factor-A, upregulation of adhesion molecules, and reactivation of the hypoxia-angiogenesis program [11,29]. All of these can lead to penetration of inflammatory cells or toxic substances from the vascular system to the CNS parenchyma, and cause rapid progression in MS.

On the other hand, high body temperature can also increase the MS symptoms. This condition is known as Uhthoff's phenom-

enon [32]. It is explained by a conduction block because of the ionic channels properties change under high temperature [33]. However, the effect of heat changes on MS can be multi-factorial. Blockage of ion channels, changes in circulation, heat shock proteins, effects of serum calcium, and unidentified humoral substances can play a part in this effect [34]. Uhthoff's phenomenon and the characteristic deterioration of MS symptoms by increased body temperature due to physical exercise may also be observed with triggering factors such as fever, hot meals, hot bath or shower, weather, menstruation, but also smoking and psychological stres [33]. Similarly, MEFV gene mutations can also raise the body temperature by increased release of IL-1β that is a potent pyrogenic cytokine, because healthy heterozygotes for MEFV mutations have higher than normal blood levels of acute phase reactants [20], and many FMF patients have continued subclinical inflammation during attack-free periods [35]. Now that the symptoms that accompany the fever are also caused by increased inflammation, MEFV mutations may exacerbate MS symptoms via production of IL-1β that is a major mediator of inflammation and fever. Probably the temperature will be higher in the CNS that is a closed area compared with the PNS and thus increased heat will enhance already existing CNS damage in MS [36].

Conclusion

In MS, inflammatory damage, apoptosis of neurons and oligodendrocytes, BBB disfunction, and Uhthoff's phenomenon, which play an important role in the pathogenesis and clinical course of the disease, can be induced by increased activation and release of IL-1β in the presence of MEFV gene mutations. Probably the potential devastating effects of IL-1β can accelerate the course of the disease. Therefore, screening for MEFV mutations in MS patients and treatment planning with IL-1β targeting drugs for the carriers seems a reasonable idea that will be a source of inspiration for scientific studies.

Competing interests

The authors declare that they have no competing interests.

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