HMGB1-TLR Signaling in Rasmussens’ Encephalitis

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Abstract

Rasmussen’s encephalitis is neurological disorder of childhood characterized by uni-hemispheric inflammation, intractable focal epilepsy and progressive cognitive and neurological deficits. Currently, the pathogenesis of Rasmussen’s encephalitis is still enigmatic and hemispherectomy is the only effective method to control the seizures associated with Rasmussen’s encephalitis. Recently data indicated that intrinsic activation of endogenous pro-inflammation high-mobility group box-1 (HMGB1) and Toll-like receptor (TLR) is involved in the development of Rasmussen’s encephalitis. Activation of HMGB1-TLR signaling plays a critical role in brain inflammation, development of epilepsy and cognitive dysfunction. Targeted therapy on HMGB1-TLR signaling might be a novel strategy with anti-inflammation, anti-epilepsy as well as improving cognitive dysfunction associated with epilepsy in Rasmussen’s encephalitis.

Keywords: Rasmussen’s encephalitis; Epilepsy; Inflammation; Cognition; HMGB1

Introduction

Rasmussen’s encephalitis is a very rare chronic progressive inflammatory neurological disorder of uncertain etiology affecting mostly children and associated with hemispheric atrophy, focal epilepsy (epilepsia partialis continua), cognitive deterioration and progressive neurological deficits, resulting from progressive loss of function subserved by the involved cerebral hemisphere [1-3]. The etiology and pathogenesis of Rasmussen’s encephalitis, in particular, the factors responsible for the characteristic of asymmetry are still elusive. Currently, hemispherectomy is the only effective method to control the seizures associated with Rasmussen’s encephalitis. Increasing experimental and clinical evidence supports a link among inflammation, epilepsy (both in terms of epileptogenesis and the long-term consequences of seizures) and cognitive dysfunction associated with epilepsy, which indicates that activation of inflammatory processes in the brain is a common feature of various epileptic disorders [4]. Recently study demonstrates that intrinsic activation of endogenous pro-inflammation high-mobility group box-1 (HMGB1) inflammatory cytokines to induce secondary inflammatory responses by acting on astrocytes [21]. Therefore, Microglia plays critical roles in establishing and maintaining inflammatory responses in the context of neurodegenerative diseases [7]. TLRs play a key role in pathogen recognition, which recognize a diverse set of pathogen-associated

HMGB1/TLR Signaling and Cognition

Brain inflammation has been implicated in the pathophysiology of several neuropsychiatric conditions. Therefore, inflammatory processes which are triggered in the brain by an epileptogenic insult may, concurrently with seizures, lead to the development of neuropsychiatric abnormalities [4]. As a crucial regulator mediating epilepsy development and brain inflammation, HMGB1/TLR signaling also has been implicated in the pathophysiology of cognitive and psychiatric phenotypes. RAGE mediated inflammatory pathway plays an important negative regulator of learning and memory. In particular, the increased RAGE signaling has been implicated in mechanisms of memory impairments in Alzheimer's disease, and RAGE is regarded as a potential therapeutic target to ameliorate cellular dysfunction and cognitive dysfunction [31]. Recent evidence indicated that HMGB1 and its corresponding receptors are upregulated in the inflammation pathway in epileptic tissue and may play a crucial role in the development and perpetuation of seizures and cognitive dysfunction associated with epilepsy [4,15]. To elevate the brain levels of HMGB1 via intracerebroventricular administration has been proven to precipitate seizures and disrupted object memory mediated by either TLR4, or RAGE [32]. Refractory focal seizures and cognitive deterioration are the clinical features of Rasmussen's encephalitis, a rare progressive inflammatory disorder of uncertain etiology [1,2]. Upregulation of HMGB1, TLR4 and RAGE in reactive microglia, reactive astrocytes, neurons and vascular endothelial cells has been demonstrated in the brain lesion area of Rasmussen's encephalitis. Therefore, HMGB1-induced overstimulation of RAGE or TLR4 might contribute to memory deficits in Rasmussen's encephalitis.

Currently, we still have no clear answer for the etiology and pathogenesis of this destructive inflammatory response in Rasmussen's encephalitis; in particular, the factors responsible for the characteristic of asymmetry are still elusive. We are uncertain of the possible initial antigens to trigger the inflammatory response and why the process is unilateral. So far, hemispherectomy is the only effective method to control the seizures associated with Rasmussen's encephalitis. To date anti-inflammatory therapy has not produced lasting responses in Rasmussen's encephalitis, such as corticosteroids pulses and intravenous immunoglobulins. Therefore, imperfectly effective immunological interventions might unacceptably postpone hemispherectomy. Evidence demonstrated HMGB1-TLR pathway in activation of immune and endothelial cells in the pathogenesis of Rasmussen's encephalitis. Therefore, perhaps more specifically targeted therapy such as targeting on HMGB1-TLR might produce lasting and promising clinical responses.

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