The toll (like receptor 3) to the pathogenesis of herpes simplex encephalitis

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Herpes simplex virus 1 (HSV-1) is a ubiquitous human virus that infects the majority of the world's population. Following primary infection, it becomes latent in neurons in cranial and dorsal root ganglia, from which periodic reactivations typically result in oral and less commonly genital mucosal lesions. In contrast to mucosal disease, herpes simplex encephalitis (HSE), the most serious CNS manifestation, is a rare consequence of HSV's interaction with its human host. Nonetheless, HSE is the most common cause of acute sporadic viral encephalitis, occurring with a frequency of 1–4/million in the Western world.[1] Why so few people develop HSE despite the widespread exposure to HSV remains a mystery.

HSE can result from either primary infection with HSV or from reactivation of latent virus, with childhood cases typically reflecting primary exposure. The pathway by which HSV, either at primary infection or during reactivation, enters the nervous system, and the sites from which viral reactivation (ganglionic vs brain tissue) leads to HSE, have not been established. Infection with HSV, and other neurotropic viruses, triggers innate and adaptive (T-cell and antibody) immune responses, with the former occurring immediately and playing a key role in the initial control of viral replication and spread.

Mammalian cells, including neurons, have developed complex danger-sensing mechanisms to detect pathogens based on the presence of specific molecular patterns (pathogen-associated molecular patterns [PAMPs]).[2] These pattern recognition receptors (PRRs) differ by the site at which they sense PAMPs (e.g., at the cell surface vs the cytosol) and by the specificity of the PAMP signal that triggers their activation. Viruses are typically recognized by PRRs due to the presence of PAMPs: double-stranded (ds) RNA, an intermediary during viral replication; uncapped single-stranded RNA, a template for viral protein transcription; viral genomic DNA with unmethylated CpG repeats; and glycoproteins that form recurring components of viral surfaces. Toll-like receptor 3 (TLR3) is a PRR[3] triggered by viral dsRNA, leading to the activation of specific transcription factors, which stimulate production of antiviral interferons (IFNs) and other cytokines. IFNs in turn induce a complex program of hundreds of genes, and identifying the key IFN-stimulating genes responsible for immunity against individual viruses is only beginning to be deciphered.[4] The plot thickens since in the CNS different cell types (neurons vs astrocytes and microglia) vary in their innate immune responses, and the neuronal reaction differs according to brain region.[5] Further, neurons from different brain regions may vary in their innate immune signaling in response to neurotropic viruses.[5] Thus, regional variation may contribute to the distinct neurotropism and patterns of CNS injury of HSV and other neurotropic viruses.

Moreover, proinflammatory cytokines have complex effects during viral infection that vary in the periphery and the CNS, with actions that facilitate viral clearance, while others contribute to host cell injury. For example, mice lacking TLR3 may have either worse or less severe CNS disease based on the specific virus and the challenge model.[3] In the case of HSV, mice lacking TLR3 or the key intermediary signaling molecule TRIF typically develop more severe CNS infection after HSV challenge.[6,7]

The importance of innate immunity in the control of human HSE was suggested through study of HSE in children with genetic defects that shared the common feature of encoding proteins involved in TLR3-IFN signaling pathways (reviewed in reference 3). In this issue of *Neurology*®, these international investigators extended their studies to examine the sequence of the *TLR3* gene in 120 patients with HSE. In 6 (5%), a total of 5 new *TLR3* mutations were identified.[8] Computational analysis (in silico study) suggested that 3 of these 5 mutations were likely to disrupt TLR3 function (2 were not). This analysis was followed by meticulous in vitro work confirming the in silico assumptions: when these mutations were stably expressed in cells, the 3 suspected mutations disrupted TLR3's function while the remaining 2 did not. Moreover, the expression of IFNs β and γ and interleukin-6 was almost abolished in fibroblasts derived from the 3 patients with predicted functional

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TLR3 mutations, and HSV replication was enhanced in these cells.

Being present in only a fraction of patients with HSE, do these findings have a broader implication? What predisposes to HSE in the 114/120 patients with normal TLR3? The observation that other genes associated with innate immunity were defective in some patients with HSE having normal TLR3 (summarized in reference 3) suggests that inborn innate immunity defects at large predispose to HSE. Nevertheless, the unique significance of TLR3 may be discerned: in those with TLR3 dysfunctional mutations, recurrences of HSE were more prevalent than in those with no such mutations (67% vs 10%).

In one patient with a deleterious *TLR3* mutation, the first HSE episode took place at 8 months and the second at age 35 years, and in a second patient, 3 episodes happened at 2.5, 22, and 28 years of age. Clearly something else is required to enable HSE besides a TLR3 abnormality. These may include environmental, pathogen, and host factors, alone or in concert.

The existing studies identifying TLR3-IFN signaling defects as a host susceptibility factor in HSE focus almost exclusively on pediatric populations, and it remains to be determined if the results also apply to adult and elderly patients in whom the prevalence of HSV increases progressively as a cause of encephalitis of identified etiology.

Do the current observations have a therapeutic implication? For example, genetic variation in the IFN-associated gene *OAS1* is a risk factor in humans for West Nile virus neuroinvasive disease and infection,[9] and theoretically αIFN could be added to antiviral therapy in cases deficient in TLR3-IFN signaling. To date, trials of type I IFNs in viral encephalitis have not shown benefit,[10] but no studies have focused on HSE or on treatment in subsets of patients with identified innate immune defects. The small number of patients with such an abnormality might render such a trial unfeasible.

AUTHOR CONTRIBUTIONS

I. Steiner: drafting/revising the manuscript, analysis or interpretation of data. K. Tyler: drafting/revising the manuscript, study concept or design, analysis or interpretation of data.

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