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Chapter 111

Mendelian predisposition to herpes simplex encephalitis

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INTRODUCTION

Herpes simplex encephalitis (HSE), which is typically caused by herpes simplex virus 1 (HSV-1) in patients over the age of 3 months (Nahmias et al., 1982; Aurelius et al., 1993; Dennett et al., 1997), is the most common sporadic viral encephalitis in the Western world (Whitley and Kimberlin, 2005). The estimated incidence of HSE is between two and four individuals per million per year (Skoldenberg et al., 1984; Najioullah et al., 2000; Puchhammer-Stockl et al., 2001). Approximately one-third of all HSE cases are due to primary infection, the most common pediatric form (Nahmias et al., 1982; Whitley et al., 1982; Skoldenberg et al., 1984; Whitley and Gnann, 2002). HSE in adults typically results from the reactivation of latent viral infection. The first evidence that HSV could infect the brain was provided by the case of a neonate with encephalitis described in 1941 (Smith et al., 1941). It remains unclear when the first case of HSE was reported in children or adolescents (Whitley and Kimberlin, 2005). The first adult case of HSE was described in 1944 (Zarafonetis et al., 1944). HSE was almost invariably lethal until the advent of acyclovir in the 1980s. Most patients now survive HSE, although many, including young children in particular, present neurological sequelae. HSE was a devastating disease of unclear pathogenesis, as HSV-1 is widespread and readily transmitted from person to person, with over 85% of adults between the ages of 20 and 40 years serologically positive for HSV-1 in a survey of over 20 countries (Nahmias et al., 1990, 2006). Moreover, HSV-1 is benign in most individuals, infecting the oral mucosa and establishing latency in the trigeminal ganglia, resulting in asymptomatic infection or recurrent herpes labialis.

The pathogenesis of HSE, which affects a small minority of HSV-1-infected individuals, has therefore long remained elusive (Baringer, 2008). No particular risk factors have been definitively demonstrated to be associated with HSE, the factors investigated including individual HSV-1 variations (Bergstrom et al., 1990; Izumi and Stevens, 1990; Sivadon et al., 1998; Norberg et al., 2004) and other environmental factors (Whitley et al., 1982; Skoldenberg et al., 1984; Whitley and Gnann, 2002). The potential contribution of human genetics to the pathogenesis of HSE was first suggested by reports of four unrelated multiplex HSE kindreds (Lerner et al., 1983; Koskiniemi et al., 1995; Gazquez et al., 1996; Jackson et al., 2002). Further support for this hypothesis was provided more recently by the discovery of a high incidence of parental consanguinity (14%) among French kindreds with HSE (Abel et al., 2010). The first attempt to decipher the molecular basis of human genetic predisposition to HSV-1 infection was reported in 2001, with apolipoprotein E (ApoE) genotypes found to be associated with HSE in one study (Alexopoulou et al., 2001), but not in another (Nicoll et al., 2001). It was recently shown that HSE may result from a novel group of HSV-1-specific, monogenic inborn errors of interferon (IFN) immunity (Casrouge et al., 2006; Zhang et al., 2007a), reviewed here.

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INBORN ERRORS CONFERRING PREDISPOSITION TO MULTIPLE INFECTIONS, INCLUDING HERPES SIMPLEX ENCEPHALITIS

Autosomal recessive STAT-1 deficiency

Intriguingly, HSE was not reported in patients with primary immunodeficiencies (PIDs) until 2003, when patients reported to lack signal transducer and activator of transcription (STAT)-1, a critical protein downstream from the receptors for IFN-α/β, IFN-γ (Dupuis et al., 2003) and IFN-λ (Chapgier et al., 2009), were identified (Fig. 111.1). Three mutations in *STAT1* causing a complete form of autosomal recessive (CR) STAT-1 deficiency have been reported (Dupuis et al., 2003; Chapgier et al., 2006). In patients with CR STAT-1 deficiency, the 1757-1758delAG, L600P (Dupuis et al., 2003) and 1928insA (Chapgier et al., 2006) mutations lead to a loss of STAT-1 protein expression and function in the patients' cells. This results in impairment of the activation of IFN-stimulated gene factor 3 (ISGF3) in response to IFN-α/β and of gamma-activated factor (GAF) in response to IFN-γ. Clinically, patients with CR STAT-1 deficiency present a syndrome of susceptibility to both mycobacteria and viruses. Two of these patients died from viral diseases, HSE in one case (Dupuis et al., 2003). Comparisons of the infectious phenotypes of patients with CR STAT-1 deficiency and patients with MSMD, including those with IFN-γR1 and IFN-γR2 deficiency (Filipe-Santos et al., 2006; Zhang et al., 2008) and partial dominant (PD) STAT-1 deficiency (Filipe-Santos et al., 2006; Zhang et al., 2008) in particular, strongly suggest that STAT-1-deficient patients are susceptible to mycobacterial disease due to their impaired response to IFN-γ (Casanova and Abel, 2002), and are susceptible to viral diseases, including recurrent HSE in one child (Dupuis et al., 2003), due to their impaired IFN-α/β responses (Rudd et al., 2006). A partial form of recessive (PR) STAT-1 deficiency has recently been reported (Chapgier et al., 2009), in which IFN-α/β, IFN-γ, and IFN-λ signaling is impaired, but not abolished. Two affected siblings from one family have been shown to carry the g.C2086T mutation in *STAT1*. These siblings suffered from severe but curable intracellular bacterial diseases and viral diseases, including cutaneous cytomegalovirus and varicella zoster virus (VZV) infections. Interleukin (IL)-27-mediated immune responses have also been shown to be STAT-1-dependent (Chapgier et al., 2009), but the role of this cytokine in antiviral immunity has so rarely been documented (Imamichi et al., 2008) that it remains unclear. Collectively, the observations in CR STAT-1-deficient patients provided the first suggestion that isolated HSE might be due to inherited immunodeficiencies involving IFN-α/β-mediated, and perhaps IFN-λ-mediated (Chapgier et al., 2009), immunity.

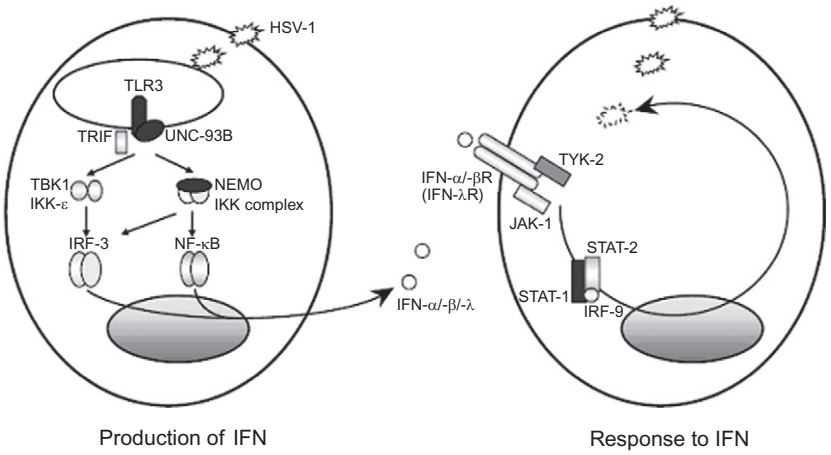


Fig. 111.1. Mendelian predisposition to HSE. Schematic representation of the production of and response to IFN-α/-β/-λ during HSV-1 infection. Viruses enter the cells and viral dsRNA is detected by TLR3. This recognition induces activation of the IRF-3 and NF-κB pathways via UNC-93B and TRIF, leading to type I or type III IFN production. TLR3, UNC-93B, and NEMO deficiencies are associated with impaired IFN production, particularly during herpes virus infection. The binding of type I or type III IFN to its receptor induces the phosphorylation of JAK-1 and TYK-2, activating the signal transduction proteins STAT-1, STAT-2, and IRF-9. This complex is translocated as a heterotrimer to the nucleus, where it acts as a transcriptional activator, binding to specific DNA response elements in the promoter region of IFN-inducible genes. STAT-1 deficiencies are associated with impaired IFN responses. Proteins for which genetic mutations have been identified and associated with particular susceptibility to HSE are shown in dark gray.

X-linked recessive NEMO deficiency

Consistent with the hypothesis that the immunity mediated by IFN-α/β, and perhaps by IFN-λ, plays a particularly important role in anti-HSE immunity, one patient with a mutation in *IKBKG* (NEMO) (Niehues et al., 2004; Puel et al., 2006) presented with recurrent mycobacterial disease and lethal HSE (Audry et al., 2011) (see Fig. 111.1). NF-κB essential modulator (NEMO), also known as IKK-γ, is a regulatory unit of the IKK complex that activates the canonical NF-κB signaling pathway, thereby regulating the expression of numerous target genes (Li and Verma, 2002). Hypomorphic mutations in *IKBKG* (NEMO) are responsible for the syndrome of X-linked anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID), associated with various developmental traits, and various infectious diseases, including pyogenic, mycobacterial, viral, and fungal diseases (Puel et al., 2004). The range of clinical features is tremendous, ranging from a life-threatening complex syndrome in infancy to adults with mild infectious diseases. Recent studies have shown that NEMO not only regulates NF-κB activation, but is also involved in the IRF-3 signaling pathway (Zhao et al., 2007), which is essential for IFN-β production, although the detailed molecular mechanism underlying the contribution of NEMO to this pathway remains unclear. One child with EDA-ID carrying the specific 110-11insC mutation in NEMO suffered from pyogenic infections, mycobacterial disease, and HSE (Niehues et al., 2004; Puel et al., 2006). This patient may have suffered from mycobacterial disease due to his impaired CD40-IL-12 pathway (Niehues et al., 2004; Puel et al., 2006). This case provided a connection between the molecular pathogenesis of HSE and NEMO. Our results showed impaired production of IFN-α/β and IFN-λ in response to both TLR3 and viral stimulation in fibroblasts and blood cells from this patient (Audry et al., 2011). In this patient with NEMO deficiency, the impaired production of IFN- α, -β, and -λ may account for the occurrence of HSE. Other patients carrying different mutations in NEMO have not been reported to suffer from HSE, whereas some developed curable viral infections (J.L. Casanova, unpublished data). Investigations of the pathways responsible for the induction of IFN-α, -β, and -λ in these NEMO-deficient patients may help to determine why HSE occurred in one of the reported NEMO-deficient patients but not in others. HSE has not been observed in other PIDs, but the occurrence of HSE in STAT-1- and NEMO-deficient patients also presenting mycobacterial disease strongly suggests that the human innate immune system is involved in protective immunity to HSV-1 in the central nervous system (CNS), and indicates that the production of or response to IFN-α, -β, and -λ probably plays an important role in HSE.

INBORN ERRORS CONFERRING PREDISPOSITION TO ISOLATED HSE

Autosomal recessive UNC-93B deficiency

The recent identification of UNC-93B deficiency in children with isolated HSE confirmed the hypothesis that HSE may result from a novel group of HSV-1-specific, monogenic inborn errors of IFN immunity (see Fig. 111.1). The human and mouse UNC-93B proteins are transmembrane proteins located principally in the endoplasmic reticulum (Tabeta et al., 2006; Brinkmann et al., 2007). In the mouse, UNC-93B binds to the transmembrane domains of Toll-like receptor 3 (TLR3) and TLR9 (Brinkmann et al., 2007), and is required for signaling by the intracellular, nucleic acid-sensing TLRs: TLR3, TLR7, and TLR9 (Tabeta et al., 2006; Kim et al., 2008; Fukui et al., 2009). In 2006, the first genetic etiology of isolated HSE was described, with the identification of homozygous germline mutations in *UNC93B1*, in two unrelated and otherwise healthy patients suffering from HSE, from different consanguineous kindreds (Casrouge et al., 2006). The identification of human UNC-93B deficiency confirmed the requirement for UNC-93B in human TLR3, TLR7, TLR8, and TLR9 signaling (Casrouge et al., 2006). The 1034del4 and 781G>A mutations in the coding region of *UNC93B1* both result in a premature termination codon, leading to a complete loss of UNC-93B expression (due to nonsense-mediated mRNA decay) and function. TLR3 signaling was abolished in the patients' fibroblasts, as shown by the impaired production of IFN-β and -λ following stimulation with poly(I:C). Peripheral blood mononuclear cells (PBMCs) from UNC-93B-deficient patients did not respond to the stimulation of TLR7, TLR8, or TLR9, in terms of the production of IFN- α, -β, and -λ, and other cytokines tested. TLR7-, TLR8-, and TLR9-mediated IFN-α, -β, and -λ production seems to be largely redundant in human antiviral immunity, as IRAK-4-deficient patients (Ku et al., 2007) display impaired production of IFN- α, -β, and -λ following the activation of TLR7, TLR8, and TLR9, but are resistant to most common viral infections, including HSE in particular. The identification of human UNC-93B deficiency thus provided proof-of-principle that HSE may result from a monogenic trait, and the first evidence that impaired TLR3-triggered, UNC-93B-dependent, IFN-α, -β, and -λ induction may be involved in HSE.

Autosomal dominant TLR3 deficiency

TLR3 deficiency was the second genetic etiology of isolated HSE to be identified (see Fig. 111.1). The identification of TLR3 deficiency demonstrated the requirement of the TLR3–UNC-93B–IFN-α, -β, and -λ signaling

pathway for protective immunity to HSV-1 in the CNS, at least in some children, during primary infection. TLR3 is one of the 10 members of the human TLR family. It can be activated by dsRNA, an almost universal viral intermediate potentially generated during most viral infections, and induces IFN production. TLR3 was therefore thought to play a broad role in antiviral immunity. Moreover, TLR3 is the most abundantly and widely expressed TLR in human CNS-resident cells, including neurons, astrocytes, oligodendrocytes, and microglial cells (Bsibsi et al., 2002, 2006; Olson and Miller, 2004; Farina et al., 2005; Jack et al., 2005; Prehaud et al., 2005; Rivieccio et al., 2006). The induction of IFN-β has been documented in neurons, astrocytes, and oligodendrocytes upon TLR3 activation by poly(I:C) stimulation (Olson and Miller, 2004; Jack et al., 2005; Prehaud et al., 2005; Rivieccio et al., 2006). IFN-λ was recently shown to be induced by TLR3 activation in human neuronal cells (Zhou et al., 2009). HSV-1 can infect neurons, astrocytes, oligodendrocytes, and microglial cells *in vitro* (Lokensgard et al., 2001; Kastrukoff and Kim, 2002; Mitchell et al., 2003; Marques et al., 2004, 2006; Bello-Morales et al., 2005; Prehaud et al., 2005). In 2007, a heterozygous germline TLR3 mutation was identified in two unrelated and otherwise healthy children with HSE from nonconsanguineous families (Zhang et al., 2007a). These two children with autosomal dominant TLR3 deficiency had the same heterozygous 1660C>T mutation (P554S) (Zhang et al., 2007a). The 1660C>T mutant allele is loss-of-function and dominant negative for the response to poly(I:C) in fibroblasts, in terms of the induction of IFN-β and -λ. Various types of TLR3-expressing cell from patients, including fibroblasts, have an impaired response to poly(I:C). The production of IFN-β and -λ by fibroblasts in response to stimulation with poly(I:C), HSV-1, and VSV was found to be impaired, as in UNC-93B-deficient fibroblasts. Moreover, higher viral titers and higher levels of cell death following HSV-1 and VSV infection were observed in both TLR3-heterozygous fibroblasts and UNC-93B-deficient fibroblasts complemented with IFN-α and -β, and, less efficiently, with IFN-λ. Impaired TLR3 signaling thus results in abnormally weak IFN- α, -β, and -λ production, higher levels of viral replication, and higher levels of virus-induced cell death in patients' fibroblasts. By inference, this provides a plausible mechanism for the pathogenesis of HSE in the CNS of these patients.

CONCLUDING REMARKS AND PERSPECTIVES

These findings have provided proof-of-principle that HSE may result from a new group of single-gene immunodeficiencies, at least in some children. The UNC-93B-dependent, TLR3-mediated production of IFN-α, -β, and -λ seems to be critical for protective immunity to HSV-1 in the CNS of children. We expect other novel genetic deficiencies involving the TLR3-mediated or IFN-responsive signaling pathways to be identified in other patients with HSE. The CR STAT-1-deficient patients reported suffered from HSE or other viral infections (Dupuis et al., 2003; Chapgier et al., 2006), suggesting that STAT-1 deficiency in humans may confer a broad predisposition to various viral infections, due to the particular importance of STAT-1 in IFN response pathways. The lack of HSE in CR TYK-2-deficient and PR STAT-1-deficient patients (Minegishi et al., 2006; Chapgier et al., 2009; J.L. Casanova, unpublished data) suggests that the intact or residual responsiveness to IFN-α/β or IFN-λ in CR TYK-2-deficient or PR STAT-1-deficient cells may provide protection by controlling HSV-1 infection in the CNS. Alternatively, the clinical penetrance of susceptibility to HSE may be low in patients with these deficiencies. Most HSE patients, including the reported UNC-93B- and TLR3-deficient patients (Casrouge et al., 2006; Zhang et al., 2007a), are not susceptible to other infections, or even to HSV-1 infections outside the CNS (Whitley, 2006). TLR3-independent IFN responses to dsRNA in some cells types, including dendritic cells (Zhang et al., 2007a), and TLR3-independent IFN responses to other viral intermediates may confer protection against a wide range of viruses in TLR3- and UNC-93B-deficient patients (Meylan and Tschopp, 2006; Zhang et al., 2007b). However, conclusions are limited by the small number of UNC-93B- and TLR3-deficient patients studied, potentially resulting in an ascertainment bias. No definitive conclusions can yet be drawn concerning the infectious phenotypes of UNC-93B- and TLR3-deficient patients. Nevertheless, the restricted lesions observed in the CNS and the resistance to other infectious agents in most patients with HSE suggest that the pathogenesis of HSE involves HSV-1-specific, CNS-specific, TLR3-dependent IFN immunity, at least in the course of primary HSV-1 infection in some children.

These results have important implications for treatment, as at least some patients with would probably benefit from treatment with recombinant IFN-α in addition to acyclovir (Casrouge et al., 2006). An interesting unresolved question concerns the role of the different IFN-α, -β, and -λ subtypes in anti-HSV-1 immunity. The IFN subtypes may be of importance, providing further indications for IFN treatment in patients with HSE. The identification of mutations affecting molecules connecting the receptors for IFN-α/β or -λ with STAT-1 activation, or affecting the receptors themselves, in patients with or without HSE, may be particularly important. It is also interesting that four of the seven TLR3-deficient

individuals and one of the three UNC-93B-deficient individuals did not develop HSE, despite proven HSV-1 infection (Zhang et al., 2007b). The incomplete clinical penetrance of HSE in TLR3- and UNC-93B-deficient individuals provides an explanation for the sporadic occurrence of HSE. The clinical penetrance of HSE in CR STAT-1 deficiency and X-linked recessive NEMO deficiency is unclear, as the serological status for HSV-1 of the few other CR STAT-1 patients identified is either unknown (Dupuis et al., 2003) or these patients have tested negative (Chapgier et al., 2006). The recently reported two PR STAT-1-deficient patients and PR TYK-2-deficient patients did not suffer from HSE (Minegishi et al., 2006; Chapgier et al., 2009; J.L. Casanova, unpublished data), possibly due to an incomplete clinical penetrance of susceptibility to HSE in STAT-1 or TYK-2 deficiency, or to the residual IFN responsiveness of cells resident in the CNS. In any case, age at infection may be a key factor governing the development of HSE in genetically predisposed individuals, as suggested by the genetic epidemiological survey of French cases, because age at onset of HSE was earlier than expected based on data for age at HSV-1 primary infection (Abel et al., 2010). Finally, the lack of identified genetic deficiencies, including UNC-93B deficiency and TLR3 deficiency, in most other HSE patients — including adult patients with HSE, in whom the pathogenesis of HSE may be different from that in pediatric cases as pathogenesis involves viral reactivation (De Tiège et al., 2008) — makes it particularly interesting to explore other possible genetic disorders in these patients, whether concerning the TLR3–UNC-93B–IFN-α, -β, and -λ signaling pathway or other systems. Future genetic studies based on positional cloning and biological studies based on functional screening will undoubtedly provide additional insight into the pathogenesis of HSE, by identifying more clearly the molecules and cells involved in immunity to HSV-1 in the CNS, in both children and adults.

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