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## Herpes simplex virus encephalitis of childhood: inborn errors of central nervous system cell-intrinsic immunity

Shen-Ying Zhang<sup>1,2,3,@</sup>

<sup>1</sup>St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA

<sup>2</sup>Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U.1163, Necker Hospital for Sick Children, France, EU

<sup>3</sup>Paris University, Imagine Institute, Paris, France, EU

### Abstract

Herpes simplex virus 1 (HSV-1) encephalitis (HSE) is the most common sporadic viral encephalitis in Western countries. Over the last 15 years, human genetic and immunological studies have provided proof-of-principle that childhood HSE can result from inborn errors of central nervous system (CNS)-specific, cell-intrinsic immunity to HSV-1. HSE-causing mutations of eight genes disrupt known (TLR3-dependent IFN- $\alpha/\beta$  immunity) and novel (dependent on DBR1 or snoRNA31) antiviral mechanisms. Monogenic inborn errors confer susceptibility to forebrain (TLR3-IFN or snoRNA31) or brainstem (DBR1) HSE. Most of these disorders display incomplete clinical penetrance, with the possible exception of DBR1 deficiency. They account for a small, but non-negligible proportion of cases (about 7%). These findings pave the way for the gradual definition of the genetic and immunological architecture of childhood HSE, with both biological and clinical implications.

### Introduction

Herpes simplex virus 1 (HSV-1) encephalitis (HSE) is the most common sporadic viral encephalitis in Western countries and, perhaps, worldwide. The causal role of HSV in HSE was established in 1941 (Smith et al. 1941). HSE is considered the most severe clinical form of infection with HSV-1, an almost ubiquitous, and typically innocuous virus. HSV-1 is a double-stranded enveloped DNA virus. It enters the body via the oral or nasal epithelium and infects neurons, subsequently establishing latency in the trigeminal (TG) sensory ganglia (Smith 2012). More than 85% of adults worldwide have antibodies against HSV-1, which causes asymptomatic infection or benign, self-healing disease in most individuals, with gingivitis and stomatitis during primary infection and herpes labialis during reactivation

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@ shzh289@rockefeller.edu.

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(Whitley 2002; Whitley 1993). In about 1~2/10,000 infected individuals of all ages, HSV-1 invades the central nervous system (CNS) via the olfactory bulb, causing forebrain HSE (~95% of cases) or, more rarely, via the TG nerves, causing brainstem HSE (~5% of cases) (Abel et al. 2010; Jubelt et al. 2011; Whitley 2006, 2015). In general, people suffer from HSE are otherwise healthy individuals, who are not particularly susceptible to other clinical forms of HSV-1 infection. No viral dissemination to the bloodstream or tissues other than the brain has been reported during the course of HSE (Gnann and Whitley 2017; Whitley 2015). About one third of HSE cases occur in children, with incidence peaking between the ages of three months and six years, earlier than would be expected if the risk were independent of age at primary infection with HSV-1 (Abel et al. 2010; Hjalmarsson et al. 2007; Kelly and Kroll 2004; Kohl 1988, 1998; Raschilas et al. 2002; Schlesinger et al. 1995; Whitley 2002). HSE is fatal in more than 70% of the patients if untreated, and most acyclovir-treated survivors present mild to severe neurological sequelae (Campbell et al. 1982; Stahl and Mailles 2019). Beyond identification of the causal virus, the pathogenesis of HSE has long remained unclear.

In the early 2000s, it was hypothesized that childhood HSE might result from single-gene inborn errors of immunity to HSV-1 in the central nervous system (CNS) (Alcais et al. 2010; Casanova 2015a, b). HSV-1 causes HSE in only a small proportion of HSV-1-infected individuals, and no HSE epidemics are observed, strongly suggesting a key role for inherited or acquired host susceptibility to HSV-1 in the pathogenesis of this condition. Moreover, although HSE is almost always sporadic, as opposed to epidemic or familial, four multiplex kindreds with an interval of several years between HSE cases have been reported (Gazquez et al. 1996; Jackson et al. 2002; Koskiniemi et al. 1995; Lerner et al. 1983). Furthermore, a high frequency of consanguinity among the parents of children with HSE was reported in a retrospective French survey (12%) (Abel et al. 2010). These findings suggested that HSE may be genetic, at least in some children. Remarkably, HSE has not been reported in children with AIDS or conventional PIDs, such as lymphopenia, agammaglobulinemia, or neutropenia, suggesting that inborn errors of leukocytes are unlikely to be causal (Notarangelo et al. 2006; Ochs 2007). Moreover, very rare cases of “syndromic” HSE have been observed in combination with mycobacterial diseases, in a child with autosomal recessive (AR) STAT1 deficiency (Dupuis et al. 2003), and a child with a *NEMO* mutation (Audry et al. 2011; Niehues et al. 2004; Puel et al. 2006). Both disorders impair cell-intrinsic immunity in leukocytes and, probably, in all other cell types. The cells of the STAT1-deficient patient displayed impaired responses to interferon (IFN) IFN- $\alpha/\beta$ , IFN- $\lambda$  and IFN- $\gamma$  (Chapgier et al. 2009; Chapgier et al. 2006; Dupuis et al. 2003), whereas the cells of the patient with the *NEMO* mutation displayed poor IFN- $\alpha/\beta$  and IFN- $\lambda$  production (Audry et al. 2010). These observations suggested that human genetic defects affecting intrinsic immunity in the CNS, probably related to IFN-mediated antiviral defense, may underlie HSE, at least in some children. This led to the discovery of human genetic lesions underlying the typical form of isolated childhood HSE.

## Inborn errors of TLR3 immunity and forebrain HSE

Toll-like receptor 3 (TLR3) is an endosomal receptor of dsRNA (Alexopoulou et al. 2001), and an inducer of IFN- $\alpha/\beta$  and - $\lambda$ . It is highly conserved across vertebrate species (Mikami

et al. 2012) and has evolved under strong purifying selection in humans (Barreiro et al. 2009). Upon ligand binding, TLR3 recruits a single adaptor, TRIF, inducing the production of antiviral cytokines, including IFN- $\beta$ , IFN- $\lambda$ , and inflammatory cytokines, such as TNF- $\alpha$  and IL-6, through the activation of transcription factors, including IRF3 and NF- $\kappa$ B (Kawai and Akira 2006). Genetic studies of isolated HSE of the forebrain led to the discovery of single-gene inborn errors of the Toll-like receptor 3 (TLR3)-dependent pathway of interferon (IFN)- $\alpha/\beta$  and - $\lambda$  induction, with mono- or biallelic mutations of six TLR3 pathway genes (*TLR3*, *UNC93B1*, *TRIF*, *TRAF3*, *TBK1* or *IRF3*) (Andersen et al. 2015; Casrouge et al. 2006; Guo et al. 2011; Lim et al. 2014; Perez de Diego et al. 2010; Sancho-Shimizu et al. 2011; Zhang and Casanova 2015; Zhang et al. 2007) (Table 1). These findings, together with the previous observation of syndromic HSE in patients with X-linked recessive (XR) NEMO deficiency (Audry et al. 2011) or AR complete STAT1 deficiency (Dupuis et al. 2003), suggested that TLR3-dependent IFN- $\alpha/\beta$  and/or - $\lambda$  immunity is crucial for host defense against HSV-1 in the CNS. It has also been suggested that other mutations of these and other TLR3 or IFN pathway genes may underlie HSE in children or adults (Armangue et al. 2019; Garcia-Morato et al. 2019; Mork et al. 2015; Sironi et al. 2017; Vitturi et al. 2019). Interestingly, a few other patients with mutations in *TLR3* developed influenza A virus pneumonitis or varicella zoster virus ophthalmicus (Lim et al. 2019; Liang et al. 2019). Nevertheless, TLR3-mediated responses to dsRNA and antiviral immunity seem to be redundant in most TLR3-expressing cell types, including leukocytes in particular, probably accounting for the lack of viral dissemination during the course of HSE (Guo et al. 2011; Zhang et al. 2007). The hypothesis that CNS-specific cell-intrinsic immunity rather than leukocyte-mediated immunity is crucial for host defense against HSV-1 was tested experimentally, initially with dermal fibroblasts as surrogate cells, and then with induced pluripotent stem cell (iPSC)-derived CNS- and peripheral nervous system (PNS)-resident cells from patients with forebrain HSE and mutations of TLR3 pathway genes. Like what was shown in recently studies that mouse Tlr3 is required for responses to HSV in neurons and astrocytes (Reinert et al. 2013; Sato et al. 2018), TLR3 pathway-deficient human fibroblasts (Casrouge et al. 2006; Guo et al. 2011; Herman et al. 2012; Lim et al. 2014; Perez de Diego et al. 2010; Sancho-Shimizu et al. 2011; Zhang et al. 2007) and iPSC-derived cortical neurons and oligodendrocytes (Lafaille et al. 2012) were found to be much more susceptible to HSV-1 infection than control cells. This phenotype was rescued by the addition of exogenous IFN- $\alpha/\beta$ . By contrast, *in vitro*-differentiated human UNC-93B-deficient astrocytes or neural stem cells, and TLR3-deficient peripheral TG neurons had a susceptibility to infection similar to that of control cells (Zimmer et al. 2018). Microglial cells, the CNS-resident macrophages that have been shown to rely on the cGAS/STING pathway to orchestrate anti-HSV-1 defense in mice (Reinert et al. 2016), have not yet been tested in the setting of human immunology to HSV-1 infection. TLR3-dependent, IFN-mediated cortical neuron- and oligodendrocyte-autonomous anti-HSV-1 immunity thus appears to be crucial for host defense against HSV-1 infection in the human forebrain. These data provided a plausible cellular basis for the pathogenesis of genetically driven forebrain HSE, suggesting that cell-intrinsic immunity, as opposed to the innate and adaptive immunity mediated by leukocytes and related cells, was crucial for host defense against HSV-1 in the human forebrain (Casrouge et al. 2006; Zhang et al. 2007).

## Inborn errors of snoRNA31 and forebrain HSE

Small nucleolar RNA 31 (SnoRNA31) is a 130-nucleotide snoRNA of the H/ACA box class. The gene encoding this molecule, *SNORA31*, is highly conserved in the general population, and ubiquitously expressed in various human cell types (Jorjani et al. 2016). SnoRNA31 has only one predicted function: directing the isomerization of uridine residues to pseudouridine in position 218 of the 18S ribosomal RNA (rRNA) and position 3,713 of the 28S rRNA (Kiss 2004). Five unrelated patients with forebrain HSE have each been shown to carry one of four rare heterozygous variants of *SNORA31* (Lafaille et al. 2019) (Table 1). Studies with human pluripotent stem cell (hPSC)-derived cortical neurons showed that SnoRNA31 is produced and functional in human cortical neurons, as a CRISPR/Cas9-introduced biallelic deletion in *SNORA31* impairs pseudouridylation of the uridine residue in position 218 of the ribosomal RNA 18S in isogenic (hPSC)-derived CNS neurons. Moreover, snoRNA31 is a CNS neuron-intrinsic HSV-1 restriction factor, as CRISPR/Cas9-introduced biallelic and monoallelic *SNORA31* deletions render neurons highly susceptible to HSV-1. Accordingly, CNS cortical neurons derived from the iPSCs of patients with *SNORA31* mutations are highly susceptible to HSV-1, like those from TLR3- or STAT1-deficient patients. Exogenous IFN- $\beta$  renders *SNORA31*- and *TLR3*- but not *STAT1*-mutated neurons resistant to HSV-1 infection. Finally, transcriptomic analyses of *SNORA31*-mutated hPSC-derived cortical neurons have shown these cells to have normal responses to TLR3 and IFN- $\alpha/\beta$  stimulations, but abnormal responses to HSV-1, suggesting that AD snoRNA31 deficiency impairs intrinsic immunity by a distinctive mechanism *in vitro*, and by inference underlies HSE *in vivo* by a distinctive mechanism. The modified transcriptome level response to HSV-1 associated with snoRNA31 deficiency may affect the expression of one or more of the effectors induced by TLR3 or IFN- $\alpha/\beta$ , thereby impairing anti-HSV-1 immunity in these cells. Alternatively, snoRNA31 may interfere with HSV-1 propagation directly, by interacting with viral transcripts. Future studies should address the fine molecular mechanism by which snoRNA31 contributes to the control of HSV-1 in CNS neurons and, potentially, in other CNS-resident cell types. The discovery of AD snoRNA31 deficiency as a new genetic etiology of forebrain HSE demonstrated the essential role of human snoRNA31 in CNS neuron-intrinsic immunity to HSV-1, providing evidence that snoRNAs can be essential for host defense.

## Inborn errors of DBR1 and brainstem HSE

Debranching enzyme 1 (DBR1) is the only known RNA lariat-debranching enzyme in humans. As inferred from studies performed in yeast, DBR1 hydrolyzes 2'5'-phosphodiester linkages at the branch points of intron lariat RNAs, facilitating their rapid turnover (Arenas and Hurwitz 1987; Chapman and Boeke 1991; Jacquier and Rosbash 1986; Nam et al. 1994; Nam et al. 1997; Ruskin and Green 1985). No connection between DBR1 and host immunity to infection was known. In this context, AR partial DBR1 deficiency has recently been reported in otherwise healthy children with brainstem VE (BVE) caused by various viruses, including HSV-1, influenza B virus (IBV), and norovirus (Zhang et al. 2018) (Table 1). In most patients with devastating BVE, the brainstem is the only region of the CNS affected, suggesting that, if there is an inborn error of immunity underlying BVE, it may affect brainstem-specific immunity. Two of the five DBR1-deficient children developed

brainstem HSE. DBR1 protein levels are highest in the brainstem and spinal cord, suggesting that DBR1 deficiency disrupts immunity in brainstem-resident cells (Zhang et al. 2018). DBR1-deficient fibroblasts from the patients, whose TLR3 and IFN- $\alpha/\beta$  responsive pathways were intact, were found to contain higher RNA lariat levels than control cells, this difference becoming even more marked during HSV-1 infection. Moreover, DBR1-deficient fibroblasts were highly susceptible to HSV-1 and vesicular stomatitis virus (VSV), like TLR3- and STAT1-deficient fibroblasts (Zhang et al. 2018). The underlying molecular mechanism remains elusive. The accumulation of RNA lariats may impair virus recognition by host cells, thereby damaging cell-intrinsic defenses against viral invasion. DBR1 may also regulate the processing of some host protein-coding RNAs, non-coding RNAs (ncRNAs) (Han et al. 2017; Murray et al. 2014; Ooi et al. 1998; Petfalski et al. 1998; Sedger 2013), or viral RNA lariats (Galvis et al. 2017; Perng and Jones; Plotch and Krug 1986; Ulfendahl et al. 1989), thereby controlling cell-intrinsic defense against intracellular virus replication. Inherited DBR1 deficiency probably underlies viral infection of the brainstem through the disruption of brainstem-specific and cell-intrinsic immunity to viruses, including HSV-1. However, the cellular basis of brainstem infection in patients with *DBR1* mutations remains a matter of speculation, as iPSC-derived brainstem cells have not yet been generated and tested.

## Concluding remarks

Human genetic studies of HSE have provided proof-of-principle that TLR3 and snoRNA31 are essential for cell-intrinsic immunity to HSV-1 in the forebrain, whereas DBR1 is essential for cell-intrinsic immunity to various viruses, including HSV-1, in the brainstem (Figure 1). These observations pave the way for further studies of CNS tissue-specific, cell-intrinsic, as opposed to leukocyte-mediated, innate or adaptive immunity to HSV-1 in humans (Zhang et al. 2019). They also open up new perspectives for studies of inborn errors of immunity conferring predisposition to other types of isolated viral encephalitis (VE), such as BVE due to IBV or norovirus (Zhang et al. 2018), or CNS infection due to varicella zoster virus (Ogunjimi et al. 2017). A number of unresolved questions remain: 1) Is forebrain HSE physiologically homogeneous? The discovery of the role of snoRNA31 raises doubts about this, as no connection between this molecule and TLR3 or IFN has been established. It is possible that snoRNA31 is connected to TLR3-, IFN-inducible anti-HSV-1 immunity via hitherto unknown mechanisms. Alternatively, other TLR3- and IFN-independent molecular mechanisms may be involved in forebrain and/or brainstem HSE. 2) What is the basis of incomplete clinical penetrance for all the monogenic etiologies of forebrain HSE? This incomplete penetrance is consistent with the sporadic nature of HSE. Both host (age at infection, modifying genes) and viral factors (viral load, virus strain) may govern clinical penetrance. 3) Are there genetic etiologies, including monogenic lesions in particular, in the vast majority (~93%) of patients with forebrain or brainstem HSE for whom no genetic etiology has yet been identified? Genome-wide searches by both reverse- and forward-genetic approaches are underway. This work will build on the previous discoveries of HSE-causing genes, which will serve as anchor genes for the interpretation of genetic data. 4) Are there digenic or oligogenic inborn errors underlying HSE? Novel bioinformatic tools will be required to tackle this question. 5) Do CNS cells other than

cortical neurons and oligodendrocytes contribute to host defense against HSV-1 in the brain? The development of novel hPSC-based protocols will be required to tackle this problem. 6) Is antiviral immunity in the CNS governed principally by anatomic region of the brain (e.g. BVE due to various viruses), causal virus (e.g. HSV-1 vs. other viruses), or both? Future studies will gradually define the human genetic and immunological architecture of childhood HSE, with both clinical and biological implications.

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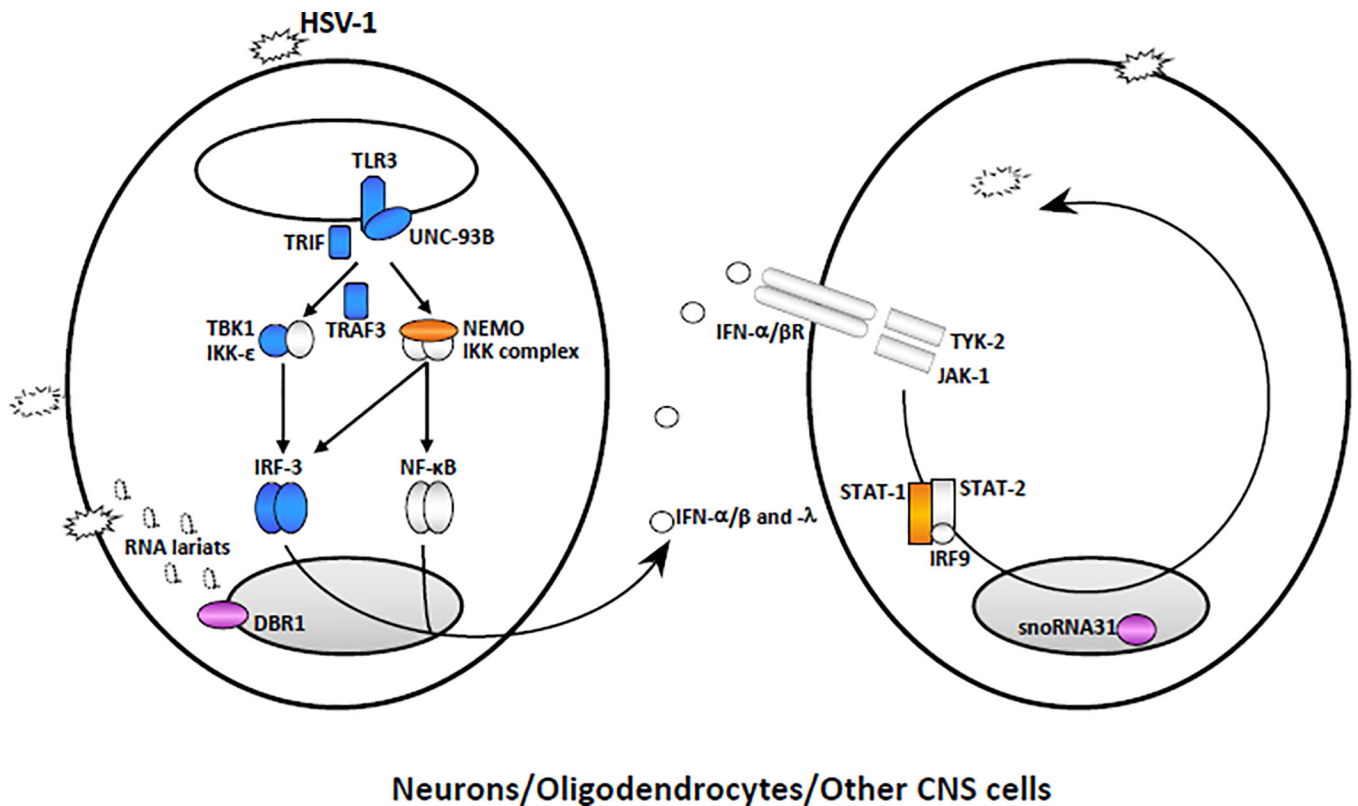
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### Neurons/Oligodendrocytes/Other CNS cells

#### Figure 1. Inborn errors of immunity conferring predisposition to childhood HSE

Monogenic inborn errors of the TLR3-IFN circuit or snoRNA31 confer susceptibility to forebrain HSE, whereas inborn errors of DBR1 underlie brainstem HSE. TLR3 signaling is initiated by the recognition of dsRNA, inducing activation of the IRF3 and NF- $\kappa$ B pathways via TRIF, leading to the production of IFN- $\alpha/\beta$  and/or IFN- $\lambda$ . Mutations of six TLR3 signaling pathway genes (*TLR3*, *UNC93B1*, *TRIF*, *TRAF3*, *TBK1*, and *IRF3*, highlighted in blue) have been found in patients with forebrain HSE. Mutations of other two genes of the TLR3-IFN circuit (*NEMO*, *STAT1*, in orange) have been found in patients suffering from HSE together with mycobacterial disease. Impaired TLR3-dependent, IFN-mediated cortical neuron- and oligodendrocyte-autonomous anti-HSV-1 immunity may underlie the pathogenesis of HSE in patients with TLR3 pathway gene defects. SnoRNA31 deficiency impairs cortical neuron-intrinsic immunity to HSV-1. DBR1 is a protein that shuttles between the cell nucleus and cytoplasm. DBR1 deficiency leads to defective RNA lariat metabolism and impaired cell-intrinsic immunity to HSV-1, despite normal cellular responses to stimulation with TLR3 or IFN- $\alpha/\beta$ . The fine molecular and cellular mechanisms by which snoRNA31 or DBR1 (in violet) deficiencies cause forebrain and brainstem HSE, respectively, remain to be dissected in detail.

**Table 1.**

Single-gene inborn errors of immunity conferring predisposition to isolated HSE

<b>Gene</b>	<b>Mode of Inheritance</b>	<b>Defect</b>	<b>Clinical findings</b>	<b>References</b>
<i>TLR3</i>	AD	Partial	Forebrain HSE	Lim et al. 2014; Zhang et al. 2007
			IAV pneumonitis	Lim et al. 2019
			VZV ophthalmicus	Liang et al. 2019
	AR	Partial, complete	Forebrain HSE	Guo et al. 2011; Lim et al. 2014
<i>UNC93B1</i>	AR	Complete	Forebrain HSE	Casrouge et al. 2006
<i>TRIF</i>	AD	Partial	Forebrain HSE	Sancho-Shimizu et al. 2011
	AR	Complete	Forebrain HSE	Sancho-Shimizu et al. 2011
<i>TRAF3</i>	AD	Partial	Forebrain HSE	Perez de Diego et al. 2010
<i>TBK1</i>	AD	Partial	Forebrain HSE	Herman et al. 2012
<i>IRF3</i>	AD	Partial	Forebrain HSE	Andersen et al. 2015
<i>SNORA31</i>	AD	Partial	Forebrain HSE	Lafaille et al. 2019
<i>DBR1</i>	AR	Partial	Brainstem HSE	Zhang et al. 2018
			BVE due to IBV, norovirus	

HSE: Herpes simplex virus 1 encephalitis; IAV: Influenza A virus; VZV: Varicella zoster virus; IBV: Influenza B virus.