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Inborn errors of anti-viral interferon immunity in humans

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Abstract

The three types of interferon (IFNs) are essential for immunity against at least some viruses in the mouse model of experimental infections, type I IFNs displaying the broadest and strongest anti-viral activity. Consistently, human genetic studies have shown that type II IFN is largely redundant for immunity against viruses in the course of natural infections. The precise contributions of human type I and III IFNs remain undefined. However, various inborn errors of anti-viral IFN immunity have been described, which can result in either broad or narrow immunological and viral phenotypes. The broad disorders impair the response to (STAT1, TYK2) or the production of at least type I and type III IFNs following multiple stimuli (NEMO), resulting in multiple viral infections at various sites, including herpes simplex encephalitis (HSE). The narrow disorders impair exclusively (TLR3) or mostly (UNC-93B, TRIF, TRAF3) the TLR3-dependent induction of type I and III IFNs, leading to HSE in apparently otherwise healthy individuals. These recent discoveries highlight the importance of human type I and III IFNs in protective immunity against viruses, including the TLR3-IFN pathway in protection against HSE.

Introduction

Since the first descriptions of interferon (IFN) as a factor interfering with virus replication [1, 2], our understanding of IFNs has significantly improved leading to the current appreciation of these cytokines in various biological functions including the induction of an antiviral state [3–5]. There are three types of IFNs classified by on their nucleotide sequence, chromosomal location, and receptor specificity [6]. Human type I IFNs, first discovered in 1957, are found as a cluster on chromosome 9 and are comprised of twelve IFN-α, one IFN-β, one IFN-ω, one IFN-ε, and one IFN-κ that utilize the IFN-α receptors 1 and 2 (IFN-αR1 and 2) [6–8] (J. Manry *et al*, unpublished). Mouse studies have demonstrated the essential role of type I IFNs, via *IFNAR1* or *IFNAR2* knockout mice [9], and of IFN-β, via *IFNB1* knockout mice, in a wide range of viral infections [10, 11]. Type II

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IFN discovered in 1965 is represented only by IFN-γ, which is encoded on chromosome 12 and uses the distinct IFN-γR1 and 2 receptors [12, 13]. To an even greater degree than in the mouse model [13, 14], human IFN-γ plays an important role as a 'macrophage-activating factor' rather than an 'IFN' [15] as patients lacking either receptor chain suffer mostly from intra-macrophagic bacterial infections, mycobacterial diseases in particular [16, 17]. Type III IFNs discovered in 2003, including IFN-λ1 (IL-29), IFN-λ2 (IL28B), and IFN-λ3 (IL28A), are encoded on human chromosome 19 and signal through the IFN-λR1 and IL-10RB receptors [18–20]. IFN-λ was shown to protect against some viral infections in mice [21, 22]. Descriptions of autoimmune diseases as a result of enhanced type I IFN immunity [23] and mycobacterial diseases as a result of decreased type II IFN immunity [16] have been reviewed elsewhere. We will herein review the known human inborn errors of immunity leading to reduced type I and/or III IFN immunity, associated with viral diseases [22].

Defects in antiviral IFNs - Broad Defects

The first inborn errors of anti-viral IFNs have been deciphered via the clinical investigation of children with herpes simplex virus (HSV)-1 encephalitis (HSE). HSE is a rare and potentially fatal infection of the central nervous system (CNS) affecting about two to four per 1,000,000 individuals per year [24–26]. Unlike the asymptomatic or benign (herpes labialis) presentation of HSV-1 infection, in the vast majority of the infected population (adult seropositivity is as high as >85%), HSE can result in up to 70% mortality if left untreated [27, 28]. Treatment with acyclovir has significantly improved survival rates however 35–62% of patients suffer life long neurological sequellae of varying severity [29]. There are two peaks of incidence, one occurring in childhood between the ages of 6 months to 3 years during HSV-1 primary infection, and another later in life (>50yrs) probably due to viral reactivation from latency [29]. In a French epidemiological survey of HSE patients it was suggested that HSE may have a strong Mendelian genetic basis, despite being sporadic, as up to 14% of the children were born to consanguineous parents [29]. HSV-1 is thought to remain localized in the CNS as systemic spread of the virus during infection has only rarely been observed [30]. There have been no reported associations of cases with a particular strain of HSV-1, suggesting that variation in virus virulence is not a major determinant of disease [31, 32]. Hence, the pathogenesis of HSE has remained elusive until the description of HSE in patients with IFN deficiencies. We will first focus on three unrelated single gene disorders underlying susceptibly to multiple viral infections, including HSE, owing to their broad impairments of IFN immunity (Table 1 and Figure 1).

STAT1

Signal transducer and activator of transcription-1 (STAT-1) is a protein involved in the transduction of cellular responses to IFN-α/β, -λ and γ, and IL-27, via the formation of two transcription factor complexes: the interferon stimulated gamma factor 3 (ISGF3) composed of STAT1-STAT2-p48/IRF9 trimers and the gamma activated factor (GAF) comprised of STAT1 homodimers [33, 34]. Heterozygous loss-of-function germ-line mutations in STAT1 impairing STAT-1 phosphorylation or DNA binding activity underlie selective impairment of the IFN-γ dependent GAF responses but intact IFN-α/β-dependent ISGF3 responses [35–37]. These patients suffer from autosomal dominant (AD) mycobacterial disease due to the impaired IFN-γ responses. First described in 2003, complete autosomal recessive (AR) mutations in STAT1 lead to a complete loss of STAT1 protein expression and consequently have no STAT1-dependent responses to IFN-γ, IFN-α/β, and –λ, leading to both mycobacterial and numerous viral diseases (Table 1) [38–41]. Two of these patients died of viral disease, one of confirmed HSE due to abolished responses to IFN-α/β and/or -λ. A milder form of partial AR STAT1 deficiency has also been reported in several patients [42,

43]. More recently, heterozygous gain-of-function mutations in STAT1 have been described in patients suffering from AD chronic mucocutaneous candidiasis (CMC). These mutations are loss-of-dephosphorylation, gain-of-function, and enhanced cellular responses to IFN-α/β, -λ and γ, and/or IL-27 are probably responsible for the poor development of IL-17-producing T cells, which are essential for muco-cutaneous immunity against *Candida albicans* [44–46]. These findings explain the fungal infections and the lack of mycobacterial or viral diseases in these patients. Overall, the various types of STAT1 mutations allowed a fine dissection of the role of STAT1-dependent IFN immunity in host response, demonstrating in particular an essential role of IFN-α/β- and/or -λ-dependent ISGF3 immunity to control various viral infections, including HSV1 infection in the CNS.

TYK2

Shortly after the description of STAT1-deficient patients with viral infections, TYK2 deficiency was reported in 2006 in a single individual with multiple viral infections and surprisingly no HSE. TYK2 is a kinase that is constitutively associated with various cytokine receptors, including IFN-αR1, in which case it is activated upon ligand-induced IFN-αR1 and IFNαR2 dimerization, allowing for the formation of ISGF3 [47]. Mouse TYK2 was initially shown to be essential for IFN-α/β signalling [48, 49] but since been shown to be involved in other cytokine response pathways including those of IL-6 and IL-12 [50, 51]. The patient with complete deficiency in TYK2 [52] displayed a broad clinical phenotype including susceptibility to *Staphylococci*, atopic dermatitis, high serum IgE, similar to hyper-IgE patients [53, 54] perhaps due to reduced IL-6 and/or IL-10 responses. He also displayed infections by *Mycobacteria* and *Salmonella*, reminiscent of patients with Mendelian susceptibility to mycobacterial disease (MSMD) [16], which was attributed to his poor cellular responses to IL-12 and subsequent impairment to upregulate IFN-γ. Finally he also suffered from recurrent cutaneous HSV-1 and *Molluscum contagiosum* infections, probably owing to his poor cellular response to IFN-α/β. Unlike the AD STAT1-deficient patients, the viral diseases manifested in the TYK2 patient were mild and limited to cutaneous infections, the reasons for which remain unclear and may reflect residual, TYK2-independent cellular responses to IFNs. The description of other TYK2 patients will be helpful in better delineating the immunological and viral phenotypes associated with this defect. In any case, TYK2 deficiency impairs at least IFN-α/β responses and confers predisposition to at least cutaneous viral diseases.

NEMO

Nuclear factor-κB (NF-κB) essential moderator (NEMO), also known as IKK-γ, is a regulatory subunit of the IKK complex activating the canonical NF-κB signalling pathway, and operating downstream of multiple receptors including TNFRs, TCR, BCR, IL-1Rs, TLRs and the RIGI/IPS-1 pathways [55, 56]. Mutations in NEMO cause a very wide spectrum of disease ranging from incontinentia pigmenti causing in-utero lethality in hemizygous males and ectodermal abnormalities in heterozygous females [57], to various forms of X-linked recessive forms of anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) [55, 58]. Children with EDA-ID usually suffer from multiple infections by various pathogens including pyogenic bacteria, fungi, mycobacteria, and viruses [55, 58]. Pneumococcal infections are the most common infections they suffer, probably due to impaired TLR and IL-1R responses [59–61]. Mycobacterial diseases probably occur due to an impaired CD40-IL-12 pathway, leading to impaired IFN-γ mediated immunity [62]. Systemic or intestinal cytomegalovirus (CMV), adenoviral and cutaneous HSV-1 infections are the most common viral manifestations of disease (Table 1) [55, 63, 64].. Interestingly, a patient with a hypomorphic mutation in NEMO developed recurrent HSE, which led to his death [63, 65]. NEMO, unlike the previous two deficiencies,

is involved in the induction of, as opposed to the response to, type I and III IFNs following cell stimulation by various receptors. A recent report has demonstrated NEMO to be involved in IRF3 activation following viral infections [56]. Of course NF-κB activation is also important to trigger the transcription of IFNs [66–69]. This dual action of NEMO potentially explains viral susceptibility in patients carrying mutations in NEMO, via impaired type I and/or III IFN production. Fibroblasts from the HSE patient with a hypomorphic frameshift mutation in *NEMO* (110_111insC), showed impaired IFN-α/β and -λ production following viral infection or Toll-like receptor 3 (TLR3) stimulation [70]. TLR3 recognizes dsRNA of viral origin, furthermore inborn errors of TLR3 immunity underlie HSE in other patients (see below), hence this defined a plausible molecular mechanism for HSE, at least in this patient [70]. In fact 8 additional patients with different mutations in NEMO showed varying degrees of impaired IFN-α/β, -λ production but no HSE despite being seropositive for HSV-1. Hence, all NEMO patients might be potentially prone to HSE however there is incomplete clinical penetrance [70]. Whether the mutations in NEMO or other factors, genetic or environmental, account for the observed rarity of HSE in patients with NEMO mutations is unclear. The specific molecular basis of viral infections other than HSE in NEMO patients also remains elusive. In any case, the role of NEMO in regulating the induction of type I and III IFNs responses is probably associated with viral diseases and the TLR3-IFN pathway with HSE in particular.

Defects in anti-viral IFNs- Narrow Defects

NEMO, STAT1, and TYK2 deficiencies all have in common broad immunological defects affecting not only type I and III IFNs but also other cytokines. They thus confer a broad infectious phenotype including viral, bacterial as well as fungal infections. It is no surprise that these patients are susceptible to multiple viral infections as their defects lie where multiple antiviral pathways converge: STAT1 and TYK2 downstream of type I and III IFN receptors and NEMO downstream of the numerous IFN-inducing receptors. In recent years, a growing number of receptors that induce antiviral IFNs have been identified, including TLRs, retinoic acid-inducible gene-I (RIG)-like receptors (RLRs), DExD/H helicases, nucleotide-binding oligomerization domain (NOD)-like receptors, and various DNA receptors (Figure 1). Ten TLRs have been described in humans, each stimulated by different agonists [71]. TLR3, TLR7/8 and TLR9 in particular are intracellular (endosomal) and involved in the sensing of extracellular and endosomal nucleic acids, dsRNA, ssRNA and dsDNA respectively, leading to type I and III IFNs production [72, 73]. RLRs consist of RIG-I, and melanoma differentiation-associated gene (MDA)-5, and laboratory of genetics and physiology-2 (LGP2) that recognize cytosolic RNA and DNA inducing IFNs through its specific adaptor, interferon-*β* promoter stimulator (IPS)-1 (also known as MAVS, VISA or Cardif) [74–77]. NOD2 has also been shown to recognize ssRNA and produce type I IFNs in an IPS1-dependent manner [78]. Recent reports have revealed DExD/H helicases to be involved in dsRNA sensing either in a TRIF-dependent (DDX1-DDX21-DHX36) [79] or in a RLR-dependent or IPS-1-dependent manner (DDX60 and DHX9 respectively) [80, 81]. The DNA sensor RNA polymerase III indirectly induces IFNs by transcribing AT rich DNA into uncapped 5′ triphosphate–bearing RNA which then signals via the RLR-pathway [82, 83]. Finally, DNA-dependent activator of IFN-regulatory factors (DAI or DLM1/ZBP1), a PYHIN (pyrin and HIN200 domain–containing proteins; also known as p200 or HIN200 proteins) protein interferon gamma-inducible protein 16 (IFI16), and another DExD/H helicase DDX41 have all been implicated in cytoplasmic recognition of intracellular DNA, leading to type I IFN production [84–87]. They signal through stimulator of interferon genes or STING (MITA, ERIS, MPYS or TMEM173) which has itself been shown to detect cyclic di-GMP, and the kinases TANK-binding kinase 1 (TBK1) and IKK-ε [86, 88–91]. The antiviral nature of these receptors have been studied primarily in the context of mouse models of experimental infection or *in vitro* [72, 74, 78–80, 84, 85, 87, 92, 93]. This shed

light on their function in host defence in experimental conditions *in vivo*, which appeared to be relatively broad for each receptor; however their respective role in natural immunity remained elusive. Recent developments in understanding antiviral immunity *in natura*, thanks to human studies, have revealed the crucial importance of the TLR3-IFN pathway in protection against the development of HSE. Here we review the few known inborn errors of antiviral IFNs that are associated with HSE (Table 1 and Figure 1). The function of other IFN-inducing pathways, like that of the many IFN-inducible genes, remains largely unknown.

UNC-93B

In 2006, the first genetic etiology for isolated HSE was reported in two children with AR UNC-93B-deficicency [94]. UNC-93B is an endoplasmic reticulum (ER) protein that contributes to the translocation of TLRs (TLR3, 7, 8 and 9) from the ER to endolysosomes [95, 96]. The four human intracellular TLRs rarely tolerate missense or nonsense mutations suggesting that they are under strong purifying selection, unlike surface-expressed TLRs [97]. TLR7 and TLR8 are primarily involved in detection of ssRNAs, TLR9 in the detection of dsDNA and TLR3 of dsRNA, which is produced during the replication of almost all viruses including HSV-1 [71, 98]. Mouse TLR7 and TLR9 have been shown to play an important role in pDCs, contributing to a significant amount of type I IFN produced by these cells [98], however human TLR7, TLR8, and TLR9 are largely redundant in host defence against viruses, as revealed by the lack of any detectable viral diseases in patients with IRAK4 and MyD88 deficiency [59, 60, 99–101]. UNC-93B was first discovered in an N-ethyl-N-nitrosourea (ENU) mutagenesis screen, underlying the *3d* mouse mutant phenotype which displayed abolished responses to TLR3, 7 and 9 agonists as well as susceptibly to murine CMV (MCMV) infection [102]. Human UNC-93B deficiency was reported shortly after, in two unrelated HSE patients homozygous for null mutations in *UNC93B1* [94]. Similar to the *3d* mouse, the patients' peripheral blood mononuclear cells (PBMCs) failed to produce type I and III IFNs in response to TLR3, TLR7, TLR8, and TLR9 agonists. The patients' fibroblasts also showed no production of type I or III IFNs (specifically IFN-β and IFN-λ1/3) following stimulation with the TLR3 agonist polyinosinic-polycytidylic acid (poly(I:C)) or following infection with vesicular stomatitis virus (VSV) or HSV-1. This viral susceptibility was complemented by the addition of recombinant IFN-α2b, suggesting the lack of IFN production was responsible for sensitivity to viral infection and demonstrating that IFN response was normal. Despite multiple TLRs affected, UNC-93B-deficient patients suffered only from HSE with no systemic or cutaneous dissemination of HSV-1, nor did they present with other severe viral infections. Hence, UNC-93B-deficiency, in combination with STAT1 and NEMO deficiencies, hinted at the essential requirement of UNC-93B-dependent IFN production for protective immunity against HSV-1 primary infection in the CNS, at least in some children. Moreover, the contribution of TLR7, TLR8 and TLR9 to disease, if any, is probably small as IRAK4- and MyD88-deficient patients, who display impaired responses to all TLRs except TLR3 do not develop HSE upon infection by HSV-1, nor any other severe viral diseases but typically present with pyogenic bacterial infections [59–61, 100]. It followed then that our attention should turn to human TLR3 as the receptor mediating the necessary protection against HSV-1 infection in the CNS.

TLR3

Shortly after the discovery of AR UNC-93B deficiency, AD TLR3 deficiency was discovered in two unrelated HSE patients carrying the same heterozygous missense mutation affecting the ectodomain of TLR3 [103]. The patients' fibroblasts displayed dominant negative properties for poly(I:C) induced type I and III IFNs production, consistent with impaired but not abolished responses to poly(I:C) [103]. Similarly, the patients' cells were

more susceptible to VSV and HSV-1 infections as assessed by IFN production, viral replication, and virus-induced cell death. The addition of recombinant IFN-α2b to the patients' cells reversed the phenotype to control levels such that the patients' cells were able to control viral induced cell mortality and replication. However, not all TLR3 expressing cells were found to have impaired poly(I:C) responses, which can be attributed to other dsRNA sensors, or residual TLR3 signalling, or both. Interestingly, another patient heterozygous for the same TLR3 mutation was subsequently reported as having coxsackie B virus myocarditis [104], suggesting that TLR3 mutations may underlie susceptibility to other viral diseases. We have also more recently identified an AR form of TLR3 deficiency, in a patient compound heterozygous for two null TLR3 alleles [105] whose fibroblasts displayed abolished responses to TLR3 whereas the patient's PBMCs, monocytes, and monocyte derived macrophages responded to poly(I:C) normally. Genome-wide transcriptome analysis using cells from this patient revealed that TLR3 is largely redundant for responses to dsRNA in leukocytes, where other dsRNA sensors may play a more significant role. Whereas the normal resistance to most viral infections in patients with AD TLR3 may result from residual TLR3 cellular responses, the occurrence of childhood HSE in an otherwise healthy adult with complete TLR3 deficiency suggests that TLR3 is largely redundant in host defence, against viruses in particular. The redundancy of TLR3 in leukocytes probably explains the narrow clinical vulnerability. Conversely, the development of HSE suggests that resident cells in the CNS, like fibroblasts, rely on TLR3 to respond to poly(I:C) and HSV-1.

TRIF

The confirmation that mutations in the TLR3 pathway underlie HSE also came recently from the discovery of Toll/IL1R (TIR) domain-containing adaptor inducing IFN-β or TRIF deficient patients [106]. TRIF, also known as TIR domain containing adaptor molecule 1 (TICAM-1), is an adaptor protein serving as the sole adaptor to TLR3 and as an alternative adaptor via TRIF-related adaptor molecule (TRAM) to TLR4 [107, 108]. Once activated by agonist-induced TLR3 dimerization (or via TLR4-TRAM), this cytosolic protein homo-oligomerizes to form a platform from which all downstream signalling events occur, ultimately resulting in type I and III IFNs and proinflammatory cytokine production [109, 110]. A recent report described an additional role for TRIF engaging in detection of cytosolic dsRNA through the DExD/H-box helicase complex, DDX1-DDX21-DHX36 [79]. TRIF-deficient mice show an abolished response to poly(I:C), resistance to endotoxic shock, and are susceptible to MCMV and vaccinia virus infections [107, 108]. Two HSE patients with TRIF deficiency were identified, one with a homozygous nonsense mutation, resulting in complete AR TRIF deficiency, and another with a heterozygous missense mutation, leading to partial AD TRIF deficiency. Similar to TLR3-deficient patients, TRIF-deficient patients' fibroblasts did not produce IFNs after stimulation with poly(I:C) and showed increased susceptibility to VSV and HSV-1 infections, highlighting the importance of the TLR3-TRIF-IFN pathway in protection against HSE. In addition, as the AR TRIF patient was a loss-of expression, loss-of-function mutation, the patient's cells also displayed impaired responses to both transfected poly(I:C) and LPS in terms of IFN induction, due to TRIF's role in the DExD/H helicase pathway and the TLR4 pathways respectively. These observations suggest that the human TRIF-dependent TLR4 and DExD/H helicase pathways are largely redundant for host defence, as this patient only suffered from HSE which can be attributed solely to the unresponsive TLR3 pathway. The impairment of these other pathways had no clinical consequence, or at least not for the moment and their role in other diseases, viral illnesses in particular, cannot be entirely excluded as the AR TRIF patient is still relatively young.

TRAF3

Discovered prior to TRIF deficiency, TNF-receptor associated factor 3 (TRAF3) deficiency was surprising at first glance because of the broad involvement of TRAF3 in both various IFN-inducing pathways and multiple TNFR superfamily responsive pathways [111, 112]. TRAF3 is an adaptor protein found downstream of the TNF receptors [111, 112], and IFN-inducing receptors including TLR3, TLR7, TLR8, TLR9, and the cytosolic dsRNA receptors RIG-I/MDA5 [112, 113]. Surprisingly, we discovered AD TRAF3 deficiency in a patient with HSE, carrying a *de novo* missense allele, which is loss-of-expression, loss-of-function, and dominant-negative, resulting in impaired but not abolished TLR3-mediated induction of IFNs and increased susceptibility to viral infections in heterozygous cells from the HSE patient [114]. Consistent with the loss-of-function observed in the TLR3-IFN mediated pathway, the TRAF3 heterozygous cells displayed impaired but not abolished function for all other TRAF3-dependent pathways, including those downstream from TNF receptors such as CD40, BAFF, and LT, and IFN-inducing receptors such as TLR7/8, and the cytosolic dsRNA pathways. At odds with the prediction and observation that human TRAF3 plays such a broad role, the patient only suffered from HSE. It is surprising that this patient has not displayed any other infectious or immunological diseases given the broad impact of the heterozygous mutation in various cell types. This suggests that the residual signalling threshold below that of predisposition to disease varies among the numerous TRAF3-dependent pathways. In other words, impaired TRAF3-dependent responses to TLR3 predisposed to HSE, whereas impaired TRAF3-dependent responses to other receptors remained clinically silent. A complete defect would be predicted to have broader clinical consequences. We cannot however exclude that such clinical consequences may appear later in life in the HSE patient. So far, TLR3-independent TRAF3-dependent IFNs (due to some residual function of TRAF3 in the patients' cells) and/or TRAF3-independent IFN production probably protected the patient against other viral infections. In any case, this experiment of Nature demonstrated that the human TLR3-and TRAF3-dependent induction of IFNs is essential for protection against HSV-1 in the CNS.

Conclusion

Broad inborn errors of antiviral IFNs, as shown by NEMO, STAT1, and TYK2 deficiencies, result in multiple viral infections in different tissues including systemic or intestinal CMV, cutaneous *Molluscum*, cutaneous herpes infections as well as HSE. Indeed, these three molecules are critical for IFN immunity, controlling cellular production of all three types of IFNs in response to the stimulation of various signalling pathways (NEMO) or cellular responses to most anti-viral IFNs, not to mention other cytokines that may also contribute to anti-viral immunity (STAT1 and TYK2). In contrast, narrow inborn errors of antiviral IFNs are thus far limited to one particular viral phenotype, HSE, due to the alteration of one particular IFN-inducing pathway, controlled by TLR3. The discoveries of UNC93B, TLR3, TRIF and TRAF3 deficiencies which all have in common a defect in the TLR3-IFN pathway strongly suggest that this mechanism is at the heart of resistance against HSV-1 primary infection in the CNS, at least in some children. Not in all children, however, as incomplete clinical penetrance was observed for all single-gene inborn errors of TLR3 immunity for which at least one relative of the proband was also genetically affected, explaining the paradoxically sporadic nature of genetically determined HSE. Multiple factors may contribute to incomplete clinical penetrance, whether environmental (infectious virus nature and amount), or host factors (genetic and even epigenetic, as suggested by the early-onset) [29].

In any case, inborn errors of TLR3-dependent IFN immunity predispose to HSE, at least in some children. TLR3 is highly expressed in the CNS, and is capable of recognizing dsRNA

intermediates produced during the life cycle of HSV-1, which with rabies virus is one of the few viruses that infect the human CNS via a neurotropic route, not crossing the blood-brain barrier [92, 115, 116]. Moreover, children with HSE are not prone to HSV-1 infections at other sites. Hence, it is tempting to speculate that TLR3 acts as a predominant dsRNA sensor in the CNS, controlling CNS-intrinsic immunity against HSV-1 in particular via its control of antiviral IFN. The selective pressure exerted by HSV-1 and other neurotropic viruses, such as rabies virus, may account for the strong signatures of purifying selection documented for human *TLR3* and *TRIF* (e.g. missense and nonsense mutations were rarely tolerated), suggesting that they played a crucial role in the survival of mankind [97, 117]. In this context, the identification of UNC93B, TLR3, TRIF, and TRAF3 deficiencies underlying HSE suggests that other genes controlling this particular pathway may be mutated in other children with HSE. The intriguing observation of a patient with viral myocarditis and AD TLR3 deficiency [104] however raises the possibility that the infectious phenotype associated with inborn errors of TLR3 immunity may be narrow in individual patients but broader at the population level, consistent with the incomplete clinical penetrance documented for both HSE and viral myocarditis.

Naturally the role of the other IFN-inducing viral sensors in host defence comes into question, as well as that of the diverse IFNs and IFN-inducible antiviral target genes. Why are there so many genes at each of these three levels? Which viral diseases would occur in individuals with inborn errors of one or another component? Reports of rare non-synonymous sequence variants in RIGI and MDA5 have been reported, several with proven defect in function but with no clear viral association reported yet [118, 119]. This suggests that these receptors might be largely redundant in anti-viral immunity. No such mutations associated with a loss of function have been reported yet for any of the other receptors. Deleterious mutations in these genes very possibly may have clinical consequences that have not yet been brought to light. It would be interesting to study these genes from an evolutionary genetic perspective and determine which ones are under purifying selective pressure [120]. A clinical genetic approach similar to that followed for HSE may also be fruitful. We hypothesize that other inborn errors of IFN immunity may underlie severe viral infections other than HSE, such as severe influenza, myocarditis, or hepatitis [121, 122]. As some of these infections show some degree of tissue specificity (like HSE restricted to the CNS), it is possible that a particular IFN-related pathway may be devoted to a specific virus or tissue, or both, in a non-redundant manner. Consistent with this notion, recent studies have associated sequence variants in IFN-λ2 with hepatitis C infection treatment response and spontaneous viral clearance in humans [123–126]. Each IFN-inducing pathway, or each IFN type and subtype, or each anti-viral IFN-inducible gene, may have selectively evolved towards protection against a particular viral infection, the diversity of IFN-inducing, IFNs, and IFN-inducible genes reflecting the diversity of viruses and tissues.

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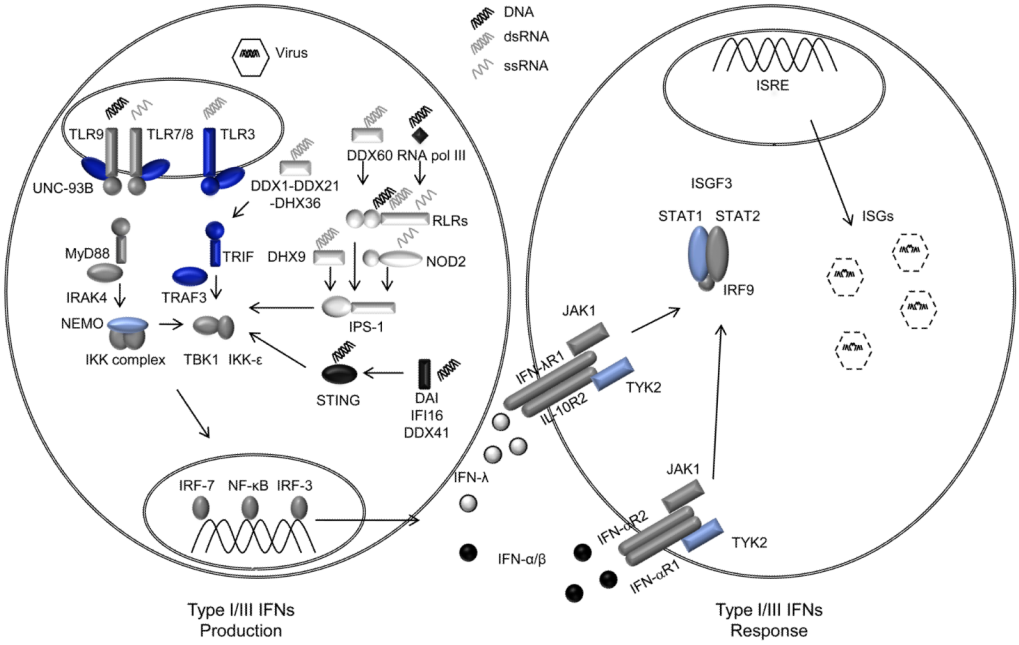

Figure 1. Human deficiencies of types I and III IFNs

Following viral infection, immune receptors engage in the recognition of viral nucleic acids via the endosomal TLRs (TLR3, TLR7/8, TLR9), the cytosolic RLRs (RIGI, MDA5, LGP2), RNA-detecting DExD helicases (DDX1-DDX21-DHX36; DDX60, DHX9), NLRs (NOD2) or DNA receptors (DAI, IFI16, DDX41, RNA polymerase III, STING) (left panel). This in turn triggers various signaling pathways leading to the activation of the transcription factors NF-κB, IRF3 and IRF7 leading to the production of the antiviral IFNs, IFN-α/β and –λ. These IFNs are detected by their respective receptors: IFN-α/β by the heterodimers of IFN-αR1 and IFN-αR2, and IFN-λ by the heterodimers of IFN-λR1 and IL-10R2. This triggers the formation of the ISGF3 transcription factor complex that binds the IFN-stimulated response element (ISRE) resulting in the induction of numerous IFN stimulated genes (ISGs) initiating an antiviral response leading to the destruction of the virus (right panel). Mutations in *NEMO*, *STAT1* or *TYK2* are associated with multiple viral infections (in pale blue) while mutations in *UNC93B1*, *TLR3*, *TRIF* or *TRAF3* are strictly associated with HSE. RNA molecules are shown in gray where as DNA is shown in black.

Table 1

Human inborn errors of antiviral IFNs

Deficiency	Viral Infections		IFN-inducing pathways*				IFNs Response*
	HSE	Other	TLR3	TLR7/8	TLR9	Cytosolic dsRNA	
STAT1	yes	CMV, EBV, HSV, *Molluscum*, Parainfluenza II, Polio III, RSV, VZV	+	+	+	NT	−
TYK2	no	CMV, HSV *Molluscum*	NT	NT	NT	NT	−
NEMO	yes	Adenovirus, CMV, HSV	−	NT	NT	+/−	+
UNC-93B	yes	−	−	−	−	+	+
TLR3	yes	Coxsackie B	−	+	+	+	+
TRIF	yes	−	−	+	+	+/−	+
TRAF3	yes	−	−	−	−	−	+

* Type I/III IFNs production (TLR3 and intracellular dsRNA pathways) and response tested in patients' SV40-fibroblasts. TLR7/8/9-induced type I/III IFNs tested in patients' peripheral blood mononuclear cells.

NT = not tested; "+" = normal; "−" = impaired; "+/−" = partial impairment.

HSV = cutaneous HSV infections