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Immunobiology of herpes simplex virus and cytomegalovirus infections of the fetus and newborn

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Abstract

Immunologic "immaturity" is often blamed for the increased susceptibility of newborn humans to infection, but the precise mechanisms and details of immunologic development remain somewhat obscure. Herpes simplex virus (HSV) and cytomegalovirus (CMV) are two of the more common severe infectious agents of the fetal and newborn periods. HSV infection in the newborn most commonly occurs after exposure to the virus during delivery, and can lead to a spectrum of clinical disease ranging from isolated skin-eye-mucous membrane infection to severe disseminated multiorgan disease, often including encephalitis. In contrast to HSV, clinically severe CMV infections early in life are usually acquired during the intrauterine period. These infections can result in a range of clinical disease, including hearing loss and neurodevelopmental delay. However, term newborns infected with CMV after delivery are generally asymptomatic, and older children and adults often acquire infection with HSV or CMV with either no or mild clinical symptoms. The reasons for these widely variable clinical presentations are not completely understood, but likely relate to developmental differences in immune responses.

This review summarizes recent human and animal studies of the immunologic response of the fetus and newborn to these two infections, in comparison to the responses of older children and adults. The immunologic defense of the newborn against each virus is considered under the broader categories of (i) the placental barrier to infection, (ii) skin and mucosal barriers (including antimicrobial peptides), (iii) innate responses, (iv) humoral responses, and (v) cellular responses. A specific focus is made on recent studies of innate and cellular immunity to HSV and CMV.

Keywords

herpes simplex virus; cytomegalovirus; neonatal immunity; fetal immunity

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Introduction

Herpesviruses infections of humans are very common and prevalent in the population. All herpesviruses establish latency in different tissues, and periodic reactivation can lead to transmission [1]. Although the majority of infections with herpes simplex virus (HSV) and cytomegalovirus (CMV) are clinically mild or even asymptomatic, primary infection in the fetal and perinatal periods can be neurologically devastating or fatal [2,3]. The precise reasons for the increased severity of disease early in life are not clear, and may involve many aspects of immune defense.

Although both HSV and CMV generally initiate infection at mucosal surfaces, they have substantial differences in their biological characteristics which are relevant to the understanding of immunity after infection with either agent. In immune-competent individuals, HSV generally infects a limited number of cell types, including mucosal and cutaneous epithelial cells and neurons, and may be clinically silent or cause ulcerative lesions [4]. Spread of the virus to other tissues is associated with an inability of the immune system to limit viral replication to the mucosa, and latent infection is largely restricted to neurons [4]. Conversely, CMV often causes a persistent primary infection, even in immune-competent adults [5], and remains latent in a variety of tissues [3]. However, although a mononucleosis-like syndrome is a recognized clinical presentation of primary CMV infection, severe disease due to CMV is almost exclusively restricted to immune-compromised individuals [3].

HSV causes neonatal infection in between 1 in 2000 [6] and 1 in 8000 [7] live births in the United States, though for unclear reasons the reported incidence is much lower in other countries [8,9]. Clinical syndromes of neonatal HSV include encephalitis (with or without skin or mucosal disease), visceral dissemination (with or without encephalitis), and isolated skin-eye-mucous membrane disease [10]. Outcomes of neonatal HSV disease are associated with the clinical syndrome at presentation, but even with effective antiviral therapy infection neonatal HSV causes mortality in more than 15% of all infants and neurologic morbidity in more than two-thirds of survivors [11]. Despite the availability of antiviral agents and efforts to prevent HSV transmission during delivery (such as Caesarean delivery), a recent study in California noted that rates of neonatal disease and HSV-associated mortality in newborns have remained stable over the past ten years [7]. Survivors of neonatal HSV-2 encephalitis appear to be at increased risk of recurrent disease [12,13], suggesting a lack of effective control of neuronal latency.

CMV is the most common known viral infection acquired *in utero*, occurring in up to 2.2% of live births in the United States [5,14]. CMV is an important cause of fetal demise and intrauterine growth retardation [15]. About 90% of congenitally infected infants are asymptomatic [16]. Congenital CMV infection is the most common acquired cause of sensorineural hearing loss [17], which may occur in patients with either clinically symptomatic [18,19] or asymptomatic [20,21] congenital infection. Congenital CMV infection is also a major cause of subsequent developmental and neurologic abnormalities [20,22]. Fulminant CMV disease in the newborn (cytomegalic inclusion disease) after intrauterine infection can lead to severe neurologic morbidity or mortality [3,22]. Infants born prematurely who acquire CMV infection postnatally are also at high risk of symptomatic infection, including after ingestion of infected breast milk [23]. Term infants infected postnatally with CMV are generally asymptomatic, highlighting the importance of immune maturation in control of disease.

Relative to older children and adults, human fetuses and newborns have an increased susceptibility to infection with a variety of different pathogens [24]. The intrauterine

environment is considered to have a general bias favoring immune tolerance [25], which may limit the ability of the fetus to fight infection [26]. During delivery, the newborn transitions from the normally sterile intrauterine milieu to an environment harboring numerous potential pathogens. Mechanical barriers to infection (skin and mucosa) may be less well developed in newborns relative to older children and adults [27]. Additionally, innate and adaptive immunity in the fetus and newborn has quantitative and qualitative differences from older children and adults, including in the numbers and function of immune cells, the function and levels of cytokines, and in the generation and levels of immune globulins [24]. Herpesviruses have evolved a variety of strategies for modulating human immune responses [28–30], which may have greater biological significance in the immunologically immature fetus and newborn.

We consider fetal and neonatal immunity in this review in the context of the important neonatal pathogens HSV and CMV, highlighting differences in disease caused by these viruses and in the responses generated. Emphasis is given to recent studies on the immunopathology of HSV and CMV infections. Although studies in both humans and mice are reviewed, we acknowledge that murine immune responses can differ from corresponding human responses, and data in mouse models may not directly extrapolate to humans.

Placental and amniotic immunity

The fetal-maternal interface—Many immune mechanisms have been described as contributing to maternal-fetal tolerance, including: (a) the lack of expression of the classical class I HLA molecules (HLA-A and HLA-B) by placental tissue [25], (b) the expression of non-classical HLA-C [31] and HLA-G [32], which may serve to inhibit maternal NK cells and induce regulatory T-cells (Treg) [33], (c) absence of class II expression in placental cells [34], (d) production of indoleamine 2,3-dioxygenase by placental cells, which may have direct inhibitory effects on maternal alloreactive T-cells [35] and indirect effects on antigen presenting cells and Treg [36], and (e) the presence at the placental interface of specialized maternal immune cells, including maternal Treg [37], $CD16^{-}$ NK cells and perhaps other decidual granular leukocytes [38]. Another important function of the placenta relevant to fetal immunity is the active transport of maternal IgG into fetal blood, which is at least partly mediated by the high expression of the neonatal Fc receptor (FcR, or CD64) in placental tissue [39].

Infections acquired *in utero* may result from ascending or transplacental viral spread. An understanding of developmental anatomy of the placenta is useful to understanding the mechanisms which may limit transplacental infection. The fetal-maternal interface is formed upon invasion of maternal uterine wall by fetally-derived placental cells [40]. Cytotrophoblastic progenitor cells differentiate to form either multinucleated syncytiotrophoblasts which are bathed in maternal blood in the floating villi, or invade the decidua to create anchoring chorionic villi. Thus, depending on the stage of pregnancy, the most direct route from maternal blood to fetus requires crossing syncytiotrophoblasts and a variable number of cytotrophoblasts to reach fetal capillary endothelium and the fetal circulation.

Ascending infection of a developing fetus requires pathogens to overcome a variety of anatomic and immune barriers. The cervical plug, maternal-fetal membranes, and antimicrobial peptides in these tissues and in the amniotic fluid may contribute to protection against vertical infection [41]. The degree to which some of these barriers (particularly antimicrobial peptides) may protect against ascending HSV or CMV infection is considered in further detail in subsequent sections.

HSV infection of the fetus—HSV rarely causes infection of the fetus; only 5% of cases of neonatal HSV are attributed to infection *in utero* [10]. Cases of intrauterine HSV infection

have been attributed to ascending infection after either viral reactivation [42] or first episode genital infection [43]. Microscopic placental involvement during intrauterine HSV infection has been described, but appears to be secondary to amnionitis [42,43].

The lack of transplacental infection due to HSV (unlike CMV) may be related to the infrequency with which HSV causes viremia. Although it was long thought that primary HSV infection did not commonly lead to viremia, recent studies have identified HSV DNA in peripheral blood of 24% of patients with primary genital HSV [44]. Viremia has not been described during recurrent HSV, and the relative lack of available virus compared to CMV may partly explain the rarity of transplacental HSV spread. Notably, HSV DNA has been detected in placental tissue derived from uncomplicated pregnancies electively terminated at different times in gestation [45,46]. Although cellular receptors for HSV appear to be present in placental tissue [47–50], if virus manages to infect placental tissue, spread to the fetus appears generally to be controlled, likely by maternal immune mechanisms.

In addition to differences in transplacental control of viral spread, another potential important difference between HSV and CMV is the site of viral latency. HSV is not known to become latent in immune cells, while CMV (discussed below) may reactivate in uterine tissue from latently infected white blood cells [45]. Perhaps reactivation of latent virus at the fetal-maternal interface also contributes to the ability of CMV but not HSV to cause transplacental infection.

Less is understood about other contributions of maternal immune responses at the placental interface to resistance to HSV infection. Even in rare cases of disseminated maternal HSV disease late in pregnancy, the infant is not always affected [51–53]. An equally puzzling question is why HSV does not cause ascending infection more frequently than it does, since an estimated 2% of women acquire primary genital infection during pregnancy [54]. Antimicrobial peptides are discussed further below, but have not been directly demonstrated to control ascending spread of HSV.

Cytomegalovirus infection of the fetus—In contrast to HSV, there is good evidence that CMV causes transplacental infection [55]. However, the precise mechanism for viral transit from mother to fetus is not known. Tissue tropism of CMV is a complex and active area of research [56]. CMV is known to infect and establish persistence within endothelial cells, smooth muscle cells, and myeloid cells [56,57]. Circumstantial evidence supports the concept that CMV may cause fetal infection via an ascending route, though hematogenous spread to the placenta is also likely [58]. Guinea pigs have a similar placental morphology to humans, and guinea pig cytomegalovirus has been shown to spread hematogenously to infect the placenta [59]. In this study, virus continued to be detected in the placenta long after clearance from the maternal blood, but only about ¼ of fetuses were infected, suggesting that the placenta may be both a site of persistent CMV infection and a barrier to viral transmission. Subsequent studies in human placentas support a similar route of viral transit from mother to fetus [60, 61].

It has been speculated that the immunologic environment of the maternal-fetal interface may contribute to reactivation of latent CMV in cells residing in the uterine wall, analogous to CMV reactivation in transplant patients [60]. Fetal cells which invade the uterine wall to contribute to placenta formation secrete IL-10 [62], which may have some local immune-suppressive activity. Latently infected maternal macrophages and/or dendritic cells (DCs) may migrate to the uterine wall in response to the presence of other pathogens, in effect carrying virus to a site at which local immune suppression may lead to reactivation and subsequent transmission to the fetus [45].

A recent study suggested that the neonatal Fc receptor may paradoxically facilitiate CMV transmission to the fetus [63]. In this model, low-avidity maternal anti-CMV antibodies bind virions via their variable regions and the neonatal FcR via the constant region, ultimately allowing FcR to transcytose complexes of virus and antibody across the syncytiotrophoblast to infect underlying cytotrophoblast cells, with subsequent viral spread to the fetus. Dysregulation of cytotrophoblast function in infected cells, including effects on cell adhesion molecules, may also contribute to viral dissemination to the fetus [64]. Conversely, in the presence of strongly neutralizing (high-avidity) maternal anti-CMV titers, nucleocapsids are retained within vesicular compartments in syncytiotrophoblast cells without evidence of viral replication [63].

Putative cell surface receptors for CMV include the epidermal growth factor receptor (EGFR) [65], the integrins α2β1, α6β1, and αVβ3 [66,67], and platelet-derived growth factor-α receptor (PDGFR-α) [68]. Cytotrophoblasts have been shown to express αVβ3 and EGFR (but not α2β1 and α6β1) [64], and infection of cytotrophoblasts appears to depend on the expression of these receptors in a spatially regulated manner [69]. Decidual cells express PDGFR-α [70], but their role in fetal infection has not been studied. It is tempting to speculate that virus which has successfully traversed the syncytiotrophoblast (either by an FcR-mediated process or some other mechanism) is capable of engaging viral receptors to allow subsequent spread to the fetus; indeed, prior authors have suggested that resistance to viral translocation across the placenta might be related to regulation of different viral receptors [69].

Other aspects of fetal-maternal immunity—The relative contributions of other immunologic aspects of maternal-fetal immunity to fetal protection against HSV or CMV infection are not well-described. Both HSV and CMV can downregulate HLA-C [71]; it could be speculated that this removes inhibition from maternal NK cells and allows for selective NK-mediated killing of virally infected cells. Indoleamine 2,3-dioxygenase (IDO) produced by placental cells is thought to contribute to maternal tolerance by degradation of the essential amino acid tryptophan, suppressing T-cell responses [35,36]. In other settings, IDO is induced by IFN-γ production and may have direct anti-HSV and anti-CMV effects [72,73]. Further research is needed to better understand how the maternal-fetal interface simultaneously allows allogeneic tolerance and protection against pathogens.

Summary—Complex and incompletely understood mechanisms protect the developing fetus from transplacental or ascending infection (Table 1). Intrauterine infection with HSV is rare, and appears to be more likely secondary to ascending infection and amnionitis than transplacental transmission. CMV infection of the fetus is much more common, and appears to most frequently occur transplacentally. CMV has several mechanisms which may contribute to its ability to cause transplacental infection, including direct effects on placental tissue.

Skin/mucosal Immunity

Both HSV [4] and CMV [5] typically initiate infection at muco-epithelial surfaces. Disease localized to the skin, eyes, and/or mucous membranes is a distinct clinical presentation of neonatal HSV [10]. HSV encephalitis in the neonate (in the absence of disseminated disease) is thought to be initiated by cutaneous or mucosal infection, followed by viral spread to the supplying sensory nerves and ultimately to the central nervous system [4]. Immunity at epithelial surfaces may be less relevant for transplacentally-acquired congenital CMV infection, but premature infants may acquire symptomatic infection via mucosal surfaces after exposure to infected breast milk. In older children and adults, CMV also generally initiates infection at mucosal sites, typically either via shedding in saliva or at genital mucosa [5].

Physical barriers to HSV and CMV infection—Skin and mucosal epithelial cells can provide a physical barrier to infection. Intact skin serves as a barrier to HSV in the neonate, as shown indirectly by the observation that invasive monitoring is a risk factor for neonatal HSV [74]. The skin of a term newborn has similar structure to adult skin (including epidermis, dermis, and subcutaneous fat), but the epidermis is thinner [75]. All skin layers are less well-developed in premature infants than term infants, conferring even higher risk for skin disruption secondary to trauma [76]. Even in a term infant, the barrier function of the stratum corneum differs from that of an adult, indicating maturation of skin barrier function in the days following birth [27]. Keratinocytes in the stratum granulosum and stratum spinosum and underlying dermal cells are the principal cell type infected by HSV, however DC in the epithelium (Langerhans cells) are also infected (Puttur F.K. et al., unpublished observations). Disruption of the stratum corneum may allow virus access to these cells in the epidermis.

Antimicrobial peptides

Tissue distribution of antimicrobial peptides: In addition to serving as a mechanical barrier to infection, skin has innate antimicrobial functions. Skin and mucosal keratinocytes produce antimicrobial peptides and proteins which can be directly protective against infection [77,78]. In addition, these peptides and proteins have less direct influences on immune responses, including promoting DC development and chemotaxis [79]. These molecules include lactoferrin, lysozyme, cathelicidin (also known as human cationic antimicrobial peptide hCAP-18 and as LL-37 for the active 37-amino acid peptide) and the β-defensins. Adult keratinocytes constitutively produce human β-defensin-1 (hBD-1). Production of hCAP-18 and hBD-2 and -3 can be induced during an inflammatory response [80]. Cathelicidins and defensins have also been detected in mucosal epithelia [81,82], ocular epithelia [83–85], and saliva [81,86].

Newborn skin and mucosal epithelia are known to contain antimicrobial peptides. Cathelicidin and hBD-2 are constitutively expressed in human newborn skin [87], and lysozyme and lactoferrin have also been found in the stratum corneum of term newborns [88]. Lysozyme is present in newborn stratum corneum at 5-fold higher levels than in adults [88], and a murine homologue of cathelicidin is expressed in the skin of newborn and embryonic mice at 10- to 100-fold higher levels than found in adult mice [87]. Fetal and newborn mice also produce cathelicidin in oral mucosal tissue [89]. The precise roles of antimicrobial peptides in defense of the newborn against HSV or CMV have not been studied in detail, but these observations suggest that these mechanisms are present early in life.

Cathelicidin and β-defensins: Cathelicidin may have antiviral activity against HSV. Indirect evidence of this comes from studies in patients with atopic dermatitis (eczema), who have diminished levels of cathelicidin in skin compared with normal subjects [90]. Skin of patients with atopic dermatitis may become secondarily infected with herpes simplex, leading to the clinical condition of eczema herpeticum [91]. Immunostaining analysis of skin biopsy samples from individuals with atopic dermatitis and a history of eczema herpeticum demonstrates lower levels of LL-39 than biopsies from individuals with atopic dermatitis without this history [78]. *In vitro* assays have demonstrated the ability of LL-39 to inhibit viral replication for both HSV-1 [83] and HSV-2 [78]. HSV-2 in explanted skin from mice with a deficiency in the murine homologue of human cathelicidin replicates to significantly higher levels than in skin explants from wild-type mice [78].

Data are less available regarding the ability of human β-defensins to protect against HSV infection. *In vitro* studies fail to show an individual effect of hBD-1 or hBD-2 on binding, entry, or replication of HSV-2, although hBD-3 and several human α-defensins have anti-HSV activity [92]. Keratinocytes are not known to produce α-defensins, though these primarily

leukocyte-derived peptides are produced in the human vaginal mucosa and contribute to the anti-HSV activity of cervicovaginal secretions [93]. The ability of combinations of natural human β-defensins to provide protection against HSV infection has not been studied in detail, though there is much active research in the use of cationic oligomers (including homologues of α- and β-defensins) [92,94,95] and non-human defensins [96] to inhibit HSV binding and replication [79].

Compared with HSV, the antiviral activity of cathelicidin and the β-defensins against CMV has received comparatively less attention. For congenital infection, these molecules may have less relevance overall. Antiviral activity against CMV has been shown for some α-defensins [97], which may participate in limiting transplacental spread.

Other antimicrobial peptides: Among the other skin and mucosa-associated antimicrobial peptides, lactoferrin and its peptic digestion product lactoferricin have received significant attention for their antiviral activity. Several *in vitro* studies testing activity of lactoferrin and/or lactoferricin against either herpes simplex or cytomegalovirus suggest inhibitory activity, possibly by interfering with cell surface binding [98–103]. The clinical significance of this activity is not known. It is worth noting that human breast milk contains many antimicrobial peptides, including lactoferrin in high concentrations [104], but that this activity does not fully prevent either HSV [105,106] or CMV [104,107] transmission via breast-feeding.

Summary—Differences in skin and mucosal epithelial integrity may influence the susceptibility of the newborn to HSV and perhaps also CMV infection. Antimicrobial peptides may have activity against HSV, and are present in newborns, suggesting a possible role in protection against HSV infection. Lactoferrin in breast milk may help to limit CMV transmission by this route.

Innate immunity

Increased understanding of the interactions between innate and adaptive immunity has been among the most important advances in immunology in the past twenty years. Reviews addressing the innate response in neonatal HSV infection published in the mid-to late-1980's focused on interferons, NK cells, antibody-dependent cellular cytotoxicity (ADCC), and the monocyte/macrophage lineage in terms of their effects on immune response to HSV [108–110]. Many recent studies have added understanding of the importance of toll-like receptors and the downstream signaling produced through these molecules to neonatal HSV and CMV responses.

Toll-like receptor signaling—There are at least ten members of the toll-like receptor (TLR) family expressed in humans, which function to sense microorganisms through detection of pathogen-associated molecular patterns [111]. Signals transmitted through TLR3, TLR2, and TLR9 have been described as contributing to the antiviral response to herpesviruses, and are considered further below.

Toll-like receptor 3: Toll-like receptor 3 binds double-stranded RNA [112], which may be produced during viral replication [113]. The potential importance of TLR3 signaling to immune defense against HSV has been recently highlighted by the connection between this pathway and susceptibility to HSV encephalitis [113,114]. These reports describe children with HSV encephalitis found to have polymorphisms in TLR3 [114] or UNC93B [113], a protein required for signaling through TLR3, TLR7, TLR8, and TLR9. This latter group of patients was found to have diminished IFN-α, IFN-β, and IFN-λ production in response to polyinosine-polycytidylic acid (poly(I:C)), a TLR3 agonist which mimics the natural TLR3 ligand dsRNA [113].

Studies of innate immunity in newborns suggest an overall general attenuation of responses to TLR ligands. Normally, ligation of TLR3 leads to DC production of type I interferons (IFN-α and IFN-β), DC maturation (including expression of MHC class II, adhesion, and costimulatory molecules), and production of proinflammatory cytokines such as IL-12 [115, 116]. Upon stimulation with poly(I:C), myeloid DCs (mDCs) isolated from human cord blood produce significantly lower levels of bioactive IL-12 and IFN-α and have diminished upregulation of the costimulatory molecules CD40 and CD80 when compared with DCs isolated from adult blood [117]. Diminished e*x vivo* production of IFN-α by newborn peripheral blood mononuclear cells (PBMCs) relative to adults has also been demonstrated after exposure to viruses [118], including HSV [119]. Although TLR3 is expressed in keratinocytes [120], genital mucosa [121], and the central nervous system (including fetal astrocytes) [122,123], the relative responses of adult and neonatal cells other than DCs to TLR3 agonists have not been assessed.

In accordance with the above-mentioned relationship between TLR3 signaling and HSV encephalitis, several studies have further clarified potential roles for TLR3 in the immune response to HSV infection. Pretreatment of murine genital mucosa with the TLR3 ligand poly (I:C) protects against subsequent genital HSV-2 challenge, with no detectable mucosal replication of virus [124,125]. This effect may be mediated by stimulation of IFN-β production, but does not appear to be due to production of IFN-α, IFN-γ, or TNF-α [126]. Cultured human female genital epithelial cells demonstrate a similar resistance to HSV-2 infection after pre-treatment with poly(I:C) [127]. The NT2-N cell line, which models postmitotic human neurons, also expresses TLR3 and responds to poly(I:C) with production of IFN-β [128]. Somewhat surprisingly, infecting NT2-N cells with HSV-1 does not lead to IFN-β production, though rabiesvirus infection does [128]. It is unclear whether this is due to HSV interference with dsRNA-sensing pathways; HSV is known to inhibit type I IFN production during acute infection, perhaps in part through expression of the virion host shutoff (vhs) protein [129, 130]. Also, acute neuronal infection may cause differing patterns of gene expression and different innate responses compared with latency or reactivation. Glial cells may also play a role in TLR3-mediated innate protection of neurons from HSV infection. Murine microglia express multiple TLRs, and respond to TLR agonists with cytokine production and upregulation of costimulatory molecules [131]. TLR3 stimulation of astrocytes with poly(I:C) induces production of IDO [132], which as discussed below and in the section on placental immunity may have direct anti-HSV and anti-CMV activity [72,73].

TLR3 signaling is thought to be involved in control of CMV infection, at least in some tissues. Poly(I:C) treatment inhibits CMV replication in cultured human ectocervical tissue and foreskin fibroblasts in an IFN-β-dependent manner [133]. Treatment of cultured human fetal astrocytes with poly(I:C) or IFN-γ inhibits CMV replication, an effect that may be mediated by IDO production [132] or by the anti-viral protein viperin [134]. Studies of murine infection with the murine version of CMV (MCMV) have shown less anti-viral activity associated with TLR3 stimulation, since the absence of TLR3 does not increase MCMV replication [135] or susceptibility of mice to infection [136].

It is not completely clear whether developmental differences in TLR3-mediated responses of newborn humans confer increased susceptibility to infection or disease after exposure to HSV or CMV. There are also no published studies which show increased susceptibility of TLR3 knock-out mice to experimental HSV infection, nor are there *in vitro* studies in which cells expressing TLR3 have been shown to be less susceptible to infection with HSV or CMV. Redundancy in innate antiviral responses may in part explain the lack of any effects.

Toll-like receptor 2: TLR2 was initially identified as a sensor of Gram-positive bacterial lipopeptides [137]. TLR2 can form heterodimers with TLR1 or TLR6 to recognize various

microbial components [138]. Although specific viral ligands for TLR2 have not been identified [139], recent studies suggest that TLR2 may be involved in innate responses to HSV and CMV infection. In contrast to TLR3, however, evidence suggests that TLR2 signaling may lead to increased pathology after HSV infection. These studies support the concept advanced by several investigators that the inflammatory response may exacerbate pathology in HSV encephalitis [140–142].

Like TLR3, TLR2 signaling has been associated with susceptibility to central nervous system HSV infection. Mice deficient in TLR2 have a diminished cytokine response and reduced mortality from neurologic disease after intraperitoneal HSV-1 infection [143], with the difference in mortality more pronounced in newborn (4 day old) mice than adults. These observations were related to increased cytokine (IL-6) and chemokine production (MCP-1) in wild-type mice relative to TLR2 knockout mice; similar observations have recently been made in a murine model of HSV eye infection [144]. Kurt-Jones et al. also showed that PBMCs from newborn humans responded to HSV with increased production of pro-inflammatory cytokines (IL-6 and IL-8) compared with adult cells [145], a finding sometimes observed in other experimental systems comparing innate responses of newborn vs. adult PBMCs [146–148]. The authors suggest that unlike the observation of dampened signaling through TLR3 in newborns relative to adults, there may be an enhanced response to signaling through TLR2, explaining the greater susceptibility of newborns to HSV disease.

Other studies support a role for TLR2 signaling in HSV infection. Polymorphisms in the human gene for TLR2 are associated with increased recurrences of HSV-2 genital lesions and increased viral shedding in humans [149]. As noted for TLR3 signaling, some murine glial cells also respond to HSV in a TLR2 dependent manner [150].

The relative importance of TLR2 signaling in HSV infection has been called into question by the *in vitro* observation that clinical isolates are rarely detected by TLR2, and only certain laboratory HSV strains are detected [139]. This study found that clinical and some laboratory HSV isolates generally exist as a collection of subspecies of viral clones, most of which do not activate TLR2, and that TLR2 and TLR9 are sequentially engaged by HSV clones recognized by TLR2. A large fraction of this TLR2-dependent recognition of HSV by DCs requires TLR9. Subspecies which do not stimulate TLR2 may still stimulate TLR9. It is also notable that in mice, delivery of TLR-2 ligands (peptidoglycan) to vaginal mucosa is not protective against subsequent HSV-2 challenge [126]. Together, these observations highlight the redundancy in innate detection and suggest the possibility of greater importance for TLR9 relative to TLR2 in detection of HSV. Importantly, control of murine infection in the brain may require synergistic activity of both TLR2 and TLR9 [151] (discussed further below).

TLR2 has been demonstrated to play a role in detection of CMV infection [152], and signaling of TLR2 in response to CMV is strongly enhanced by the co-receptor CD14. Interaction with TLR2, likely in heterodimeric form with TLR1, involves the CMV envelope glycoproteins gB and gH [153]. Clinically, a TLR2 polymorphism in liver transplant patients is associated with elevated CMV replication, and homozygosity for this polymorphism confers increased risk of CMV disease [154]. Treatment of cultured human ectocervical tissue with the TLR2 agonist lipoteichoic acid leads to inhibition of CMV replication in an IFN-β-dependent manner, but similar treatment in foreskin fibroblasts (which do not express TLR2) did not demonstrate inhibition [133]. *In vitro*, the TLR2-induced response to human CMV was recently shown to specifically lead to the production of inflammatory cytokines, while the type I interferon response was independent of TLR2 signaling [155]. A role for TLR2 signaling in fetal infection is supported by the demonstration of a TLR2-dependent inflammatory response after exposure to CMV in an *in vitro* model of human syncytiotrophoblast, which was independent of DNA transcription [156]. The importance of TLR2 in controlling CMV infection has also been shown

for mice: deficiency of TLR2 leads to elevated MCMV replication *in vivo*, which may be related to NK cell recruitment, proliferation, or sensitivity to apoptosis [157].

Toll-like receptor 9: TLR9 recognizes double-stranded DNA unmethylated at CpG motifs [158]. The relative importance of TLR9 in overall human response to HSV or CMV infections is unclear, though the lack of signaling through TLR9 by itself does not appear to produce clinically significant susceptibility to viral disease [159]. Signaling through several of the toll-like receptors, including TLR9, involves the adaptor molecule IL-1R-associated kinase 4 (IRAK-4) [111]. Humans with IRAK-4 deficiency are at increased risk for infections with some bacteria [160,161], but do not appear to be predisposed to severe viral infection [159], again suggesting redundancy in human innate anti-viral sensing. Fibroblasts and PBMCs from patients with IRAK-4 deficiency produce identical levels of type I IFNs in response to HSV (and other viruses) *ex vivo* compared with controls [159]. Despite this, PBMCs from these patients produce no type I IFNs in response to the TLR9 agonist CpG [159]. The authors note that although this evidence suggests that IRAK-4 deficiency (and therefore signaling though TLR9) may not by itself predispose to severe viral infection, very few patients have been diagnosed with IRAK-4 deficiency, leaving open the possibility that more serious viral infections may have occurred in undiagnosed cases.

Circulating human plasmacytoid dendritic cells (pDCs) detect both HSV-1 and CMV, presumably through TLR9 [162]. Cord blood pDCs stimulated with these viruses were found to produce less IFN-α than their adult counterparts, which was not attributable to lower expression of TLR9 on cord blood pDCs [162]. In mice, viral DNA from both HSV-1 [163] and HSV-2 [163,164] is detected by pDCs and conventional DCs (myeloid; cDCs) through TLR9. As noted above, in conventional DCs TLR9 appears to detect subspecies of HSV which may or may not be detected by TLR2 [139]; pDCs do not express TLR2 [165], and therefore appear to primarily use TLR9 to sense HSV. Recent studies suggest that pDCs provide the bulk of the early IFN-α response to HSV infection via TLR9 detection, while at later times other cell types produce IFN-α and IFN-β by TLR9-independent mechanisms [166]. TLR9-deficient mice are more susceptible than wild-type mice to genital challenge with HSV-2, with a significant impairment of local mucosal responses observed in the absence of TLR9 [167]. Synergistic responses via TLR2 and TLR9 after herpes simplex infection were recently demonstrated after HSV infection in mice [151]. In this study, mice lacking both TLR2 and TLR9 had lower titers of virus in the brain but not the liver after intraperitoneal infection with HSV-2, relative to single knockout mice or wild-type mice. Similarly, TLR2/9 double knockout mice were more susceptible to intravaginal infection than wild-type mice, and had higher viral titers in brain but not in vaginal washes or spinal cords. Synergy in cytokine production was not associated with the expression of TLR2 or TLR9 within different cells types, leading the authors to suggest that both receptors are necessary and act through multiple cell types for a complete response to HSV infection [151].

Susceptibility of mice to MCMV is associated with TLR9 deficiency. As noted above, *in vivo* recognition of MCMV depends on TLR9, although multiple pathways, both TLR-dependent and independent, are important in establishing adaptive immunity to MCMV [135]. Control of CMV infection in mice is related to combined signaling through TLR3 and TLR9, with TLR9-deficient mice more susceptible to mortality after MCMV infection than TLR3-deficient or wild-type mice [168]. TLR9-dependent cytokine production stimulates viral clearance by a specific population of NK cells expressing a receptor recognizing MCMV [169]. More recent studies suggest that some of the redundancy in innate sensing of MCMV may be mediated by TLR7, which has not previously been implicated in sensing of DNA viruses [170].

In addition to the observation that redundant antiviral sensing pathways may potentiate susceptibility to severe infection in individual patients, the above data are consistent with the possibility that TLR-mediated control of viral infection has differential effects within different tissues. Supporting this possibility is a recent study showing that TLR9 was necessary for IFN-α production in spleens but not livers of mice infected with MCMV [171]. Absence of TLR9 did not affect MCMV titers in liver compared with control mice, while MCMV titers in spleen were significantly higher in TLR9 knockout mice relative to wild-type.

Other innate sensors of viral infection: Increasing evidence implicates other innate sensing mechanisms capable of recognizing RNA in the antiviral response. The cytosolic RNA helicases retinoic acid-inducible gene I (RIG-I) and melanoma-differentiation-associated gene 5 (MDA5) induce type I IFN expression in response to RNA, through the mitochondrial antiviral signaling protein (MAVS) adaptor [166]. Activation of the MAVS pathway has been suggested to be important in the type I IFN responses of murine embryonic fibroblasts and perhaps macrophages after HSV infection [166], and has also been shown to affect the expression of the anti-MCMV protein viperin [172]. Innate sensors of cytosolic DNA have also been recently described [173], but their relevance to HSV and CMV infections remains to be determined.

Interaction of HSV glycoproteins with immune receptors: The viral determinants of innate immune signaling have not been well described for HSV or CMV, but recent work suggests that at least for HSV envelope glycoproteins are detected by innate sensors. Conventional DCs were demonstrated to become activated and produce IFN-α and IL-10 in response to a combination of the four essential HSV glycoproteins gD, gB, and the heterodimer gH-gL [174]. Although these proteins are involved in viral entry [175], this maturation process was independent of membrane fusion or the interaction of gD with its known receptors. Previous work suggested that HSV envelope glycoproteins may induce type I interferon secretion through interactions with the chemokine receptors CCR3 and CXCR4 [176]. Further work is needed to understand precisely how herpesvirus glycoproteins stimulate innate immune responses, and whether these processes are altered in the newborn.

Cytokine production—Effective control of viral infection in fetuses and newborns may be related to lower cytokine production relative to adults. DCs and other antigen-presenting cells from cord blood generally produce lower levels of cytokines than comparable adult cells to various stimuli *ex vivo* (reviewed in [177]). In both premature and term infants, fewer PBMC produce IFN-α in response to HSV stimulation than adults, and lower levels of IFN-α are produced on a per cell basis [119]. However, most investigators report an increased number of pDCs in cord blood relative to adult blood samples [177].

The importance of type I IFN signaling to control of HSV infection may be inferred by the observation that HSV inhibits type I IFN signaling at several levels [178,179]. Signaling through the IFNα/β receptor involves activation of Tyk2 and JAK1, which leads to phosphorylation of STAT2 and formation of a STAT1-STAT2 heterodimer, which translocates to the nucleus and associates with additional proteins to stimulate transcription of interferon-inducible genes [180]. JAK1 and STAT2 are depleted in cells infected with HSV-1 *in vitro*, due partly to the viral vhs protein [178] and to increased expression of endogenous inhibitors [179]. Human deficiency in STAT1 (which is also involved in response to type II IFN, such as IFN-γ) confers susceptibility to severe HSV infection; a patient with homozygous Stat1 mutation died from disseminated HSV with recurrent encephalitis [181]. A patient with a homozygous Tyk2 mutation was described as having recurrent skin and oral mucosal lesions caused by HSV [182]. In mice, the absence of receptors for type I IFNs [183] and the lack of Stat1 [184] leads to increased HSV replication in the nervous system and cornea.

The type I IFN response is also important to the control of CMV infection. Like HSV, both human [185] and murine [186] CMV express proteins inhibiting type I IFN production. Human CMV expresses a protein which complexes with the STAT1-STAT2 heterodimer to prevent binding to promoters of IFN-responsive genes [185], while MCMV expresses a protein which despite selectively binding STAT2 interferes with both type I and type II IFN activity [186]. *In vivo*, control of viral replication is impaired in mice lacking the receptor for type I IFN ($IFN\alpha/\beta R^{-/-}$) [186,187] and in mice lacking Tyk2 [188], relative to wild-type mice. Intracranial injection of MCMV into either newborn or adult mice leads to much higher type I IFN expression in adult brains than in newborns, and exogenous IFN-α, IFN-β, or IFN-γ, or poly (I:C) protected human brain tissue against CMV infection and cell death *in vitro* [189]. Together, although relative deficiencies in TLR signaling and type I IFN may contribute to the susceptibility of newborns and fetuses to HSV and CMV, the complexity and interrelatedness of these signaling pathways suggests that it is likely that additional host-virus adaptations and occasional susceptibility mutations remain to be discovered.

Numerous other cytokines are thought to be important for effective control of HSV and CMV infections. As alluded to in the previous section, IFN-γ is involved in control of acute neuronal infection, and has also been shown to be critical to the recall response in murine intravaginal HSV-2 infection [190] and for maintaining neuronal latency (reviewed in [191]). Additional cytokines implicated in immune control of HSV and CMV infection include TNF-α [192, 193], IL-12 [194–197], IL-18 [196], IL-23 [194], and IL-1β [193]. Again, relative roles for these cytokines in the predisposition of the fetus and newborn to HSV or CMV infection have not been clearly delineated. Recently, production of IL-6 and TNF-α were found to be reduced in newborn murine skin after infection with HSV (Jones C.A., unpublished observations). Human mutations in genes involved in some cytokine signaling pathways can predispose to severe disease from HSV, including mutations in NF-κB essential modulator (NEMO) [198]. However, patients receiving anti-TNF-α therapy are not generally thought to be at increased risk for herpesvirus reactivation [199], despite case reports of severe CMV [199] and HSV [200] disease. Studies have not been reported which assess whether patients receiving anti-TNF-α treatment shed virus more frequently or in higher amounts. Humans with mutations leading to deficiencies in IL-12 or IL-23 [201] are also not known to be at increased risk of severe HSV or CMV disease.

Dendritic cells (DCs)—The understanding of virus-dendritic cell interactions has been an intense area of research, and recent reviews have highlighted some of the complex interactions between certain populations of DCs and HSV [202,203] or CMV [204]. HSV can infect immature human cDCs but not pDCs efficiently *in vitro* [205,206], impairing their maturation [206,207] and inducing apoptosis [205,208]. Apoptosis of murine DCs after HSV infection has also been demonstrated, and appears to be induced more rapidly by HSV-2 than HSV-1 [209]. Impairment of maturation in immature neonatal murine DCs after HSV-2 infection was greater than in corresponding adult cells [209]. Murine studies have shown that infected Langerhans cells and dermal cDCs do not directly stimulate $CD4^+$ and $CD8^+$ T-cell responses after HSV-1 infection, but carry antigen to draining lymph nodes where different DC subsets act to cross-present antigen to promote T-cell activation [210,211]. Similar mechanisms of direct DC infection with subsequent apoptosis and cross-presentation of antigen by uninfected lymph node-resident DCs have been proposed for CMV [204]. Along with B cells (and to a lesser extent other APCs), mucosal cDCs are also important in recall responses to mucosal challenge in mice [190]. Recent experiments in mice have shown that neonatal DC take up HSV, perhaps with greater propensity than adult DCs (Jones C.A., unpublished observations). Neonatal DC maturation is also impaired after HSV infection, and these cells migrate out of skin to the draining lymph nodes more slowly than adult DCs (Jones C.A., unpublished observations). Little is known about the cDC response in human newborns, particularly after HSV or CMV infection.

Plasmacytoid DCs are known to respond to viral infection by producing significant amounts of IFN-α and developing antigen-presenting function to stimulate antigen-specific T cell proliferation [165,212]. Recent work has shown that human pDCs, which are not normally found in skin, migrate to dermis in response to recurrent genital HSV [213]. These cells remain resistant to HSV infection, and participate in the proliferation of HSV-specific lymphocytes. A specific role for pDCs in neonatal HSV or CMV infection has not been as well-studied, though the importance of TLR9 to both pDC responses [165] and to control of HSV and CMV infection (discussed above), and the relative deficiency in IFN-α production by neonatal pDCs [162], suggests that attenuated pDC responses may contribute to fetal and neonatal susceptibility to these viruses. Willems et al. [214] have recently reviewed differences in DC function between neonates and adults, and note the importance of the type I IFN/Flt3L signaling pathways to neonatal DC activation.

Natural killer (NK) cells—Deficiencies in NK cell responses of newborns have been proposed to be a major contributor to the severity of neonatal HSV disease [215]. These deficiencies may either be intrinsic, or related to the diminished production of type I IFNs and other NK cell-activating cytokines in newborns [216]. The activation of NK cells is complex, involving dendritic cells and cytokines such as type I IFNs, IL-12, and IL-18 [217]. Studies in mice and case reports in humans suggest that deficiencies in at least some components of NK activation may confer susceptibility to herpesvirus infection [217].

Although isolated human NK cell deficiency is rare, defects in NK number or function are commonly associated with susceptibility to herpesvirus infection [218]. A patient with altered expression of the Fc receptor for IgG type IIIA (also known as FcγRIIIA or CD16-II) was reported as suffering from recurrent infections, particularly with herpes simplex [219]. This mutation was associated with a marked reduction in spontaneous NK cell activation. A patient with apparent isolated NK deficiency had severe interstitial pneumonia associated with CMV infection, and subsequently required IV antiviral therapy after primary HSV infection [220].

The importance of the NK response in murine CMV infection has been well-described, and has been recently reviewed [221]. Resistance of different strains of mice to MCMV infection reflects the effectiveness of their NK response to infection [222]. Although NK cell-mediated killing of HSV- and CMV-infected cells is associated with downregulation of class I MHC molecules on the surface of the infected cell [223], NK cell control of MCMV infection also involves direct recognition of the viral m157 protein by the NK activation receptor Ly49H [224]. The expression of Ly49H on NK cells varies among different mouse strains, in direct relation to the susceptibility of these strains to MCMV infection [225]. A human parallel to this observation has not been identified. In addition to Ly49H, other host genetic factors influencing NK cells are also involved in resistance to MCMV [226–228]. Although several studies support the concept that neonatal susceptibility to herpesvirus infections may be related to NK cell deficits [216,229–235], the molecular details of these findings remain to be elucidated. The importance to neonatal and congenital disease of a subpopulation of NK cells known as NKT cells in early control of HSV [236–238] and CMV infection [239] also remains to be further defined.

Summary—Numerous aspects of the innate immune response influence immunity to HSV and CMV infections, any of which may contribute to some degree to neonatal susceptibility to disease (Table 2). Many innate responses appear to be redundant, making elucidation of their relative importance challenging. Data in mice and humans suggests that cytokine production mediated by TLR2 may influence immunopathology of neonatal HSV infection [143,145]. TLR2 signaling may be important to congenital CMV infection as well [152,156]. A general dampening of cytokine production in newborns may affect their response to infection

[177]. Neonatal dendritic cell and NK cell function may differ from adults after HSV (Jones, C.A., unpublished observations) or CMV infection.

Adaptive immunity

Humoral immunity—The importance of passive antibody protection to HSV and CMV disease in the fetus and newborn is well-described, and will only receive brief mention here. Pre-existing maternal humoral immunity to HSV [240] or CMV [241] is partially protective against the development of disease *in utero* or in the perinatal period. In addition to serostatus, the avidity of anti-HSV maternal antibodies is correlated with neonatal disease [242]. The human fetus can respond to *in utero* CMV infection with antibody production [243], but it is not clear to what degree (if any) these responses provide protection against disease.

Circulating antibodies may provide partial protection against neonatal HSV disease by limiting HSV dissemination in the newborn. Infants with disseminated disease were less likely to have detectable neutralizing antibody titers in the first week of illness than those with other clinical presentations of HSV disease [244]. Studies in mice showed that maternal immunization with a replication-defective virus reduced visceral dissemination in their pups after oral challenge, supporting the role of maternal IgG in limiting viral dissemination [245]. Adult mice can be protected against HSV disease with passive antibody transfer [246], but neutralizing activity did not correlate with protection against HSV disease in a mouse model of encephalitis [247]. Human vaccine studies have also shown that high titers of neutralizing antibody are unable to protect against sexual transmission [248], though this may have different pathogenesis than neonatal disease. It is also noteworthy that antibodies *per se* are not required for adequate control of HSV or CMV infections. Patients with primary antibody deficiencies [249], including agammaglobulinema (including X-linked agammaglobulinemia) [250,251], common variable immune deficiency [252], or complete IgA deficiency [252], are not known to be at risk for severe herpesvirus infections.

Cellular immunity—Early studies suggested that neonatal cellular immunity was intrinsically biased toward antigenic tolerance [253,254]. However, responses to antigenic challenge in the newborn may under certain conditions behave like those of the adult [255, 256]. Ridge et al. showed that the balance between the antigen dose and the number of antigen-presenting cells at the site of T-cell activation influences the T_H1-T_H2 bias [255], and Sarzotti et al. demonstrated that infection with high doses of a murine retrovirus biased murine newborn T-cells towards a T_H2 cytokine pattern [256]. Neonatal cellular immune responses often show a strong T_H2 bias [257–259], particularly with secondary stimulation [260]. Selective apoptosis of T_H1 cells generated during the primary response may contribute to this bias ([261] and Jones C.A., unpublished observations).

Older studies of HSV-specific responses in neonatal HSV infection have suggested diminished HSV-specific lymphocyte proliferative responses [244,262], associated with decreased IFN-γ production [262]. These studies were done by bulk stimulation with HSV antigen, and responses at the single cell level have not been measured in detail in pediatric patients using flow cytometric techniques. More recently, neonatal mice have been demonstrated to generate a paucity of both T_H1 and T_H2 cytokines relative to adult mice in response to infection with a replication-defective strain of HSV-2 [263]. Studies of the human newborn T-cell response to CMV have been conducted on cord blood samples [264–266], and although these responses can in some cases resemble those of adults, they do not correlate well with presence of disease [267].

CD4$^+$ T-cells: Investigations of the role of T-cells in the human newborn response to HSV show diminished proliferation and cytokine production in response to stimulation with HSV

antigen [244,262]. Burchett et al. compared responses of circulating lymphocytes between individuals with primary HSV infection, including 13 newborn infants, three parturient women, and nine nonparturient adults [262]. Lymphocyte proliferation and IFN-γ (but not TNF-α) production were specifically diminished in response to stimulation with HSV antigen in newborn and parturient patients compared to nonparturient adults. These responses became comparable to those of nonparturient adults only three to six weeks after symptom onset, leading the authors to suggest that delayed acquisition of specific cellular immunity may predispose to more severe clinical disease [262].

In mice, somewhat consistent with the observations of Ridge et al. [255], Evans and Jones found that neonatal mice could develop T_H1-biased $CD4^+$ T-cell responses in draining lymph nodes at lower levels of HSV challenge [263]. However, although T_H2-biased responses could be generated in adult mice at high infectious doses of replication-incompetent or inactivated virus, newborn responses (T_H1 or T_H2) were attenuated relative to the adult responses at the same conditions [263]. Notably, newborn mice infected with a strain of HSV-1 capable of only a single replicative cycle were protected against subsequent challenge, and generated antibodies, $CD4^+$ T-cells, and $CD8^+$ T-cells which responded to virus and were each separately protective against challenge with wild-type virus in transfer experiments [268].

$CD4^+$ T-cell responses to CMV in children differ from those in adults. Relative to adults, young children have lower IFN-γ and IL-2 production by $CD4^+$ T-cells on a per-cell basis, as assessed by intracellular cytokine staining in response to CMV antigen [265]. These cells also express lower levels of CD154 (CD40 ligand) than adult cells [265]. The development of this response in young infants was recently followed in a prospective cohort study in the Gambia; this study supported the above observations, but also noted no differences in responses between congenitally infected infants and those acquiring CMV postnatally [267]. Despite these observations, none of the infected children in this study were found to have CMV disease. Further studies are needed to understand the role cellular immunity may play in explaining the different clinical presentations of CMV disease and asymptomatic infection.

$CD8^+$ T-cells: The studies discussed above showing that stimulation of circulating lymphocytes from HSV-infected newborns with HSV antigen leads to diminished lymphocyte proliferation compared to adults were likely measuring primarily $CD4^+$ responses [244,262]. Information on HSV-specific $CD8^+$ T-cell responses is largely limited to studies in mice. Newborn mice infected with HSV develop a delayed $CD8^+$ T-cell response in draining lymph nodes compared with adult mice, with a lower peak activity [269]. This response is independent of HSV dose, in contrast with the findings for HSV-specific $CD4^+$ T-cells [263]. Despite the delayed and attenuated HSV-specific response, neonatal $CD8^+$ T-cells were observed to upregulate expression of activation markers *in vivo* earlier than adults, but expression of these markers was not sustained [269]. It is possible that dysregulation of the early antigen-specific $CD8^+$ T-cell response in newborns contributes to their relative difficulty in controlling HSV infection.

In CMV infection of young children, CMV-specific $CD8^+$ T-cells are present in identical frequencies and have detectable intracellular IFN-γ perforin expression production at identical levels as adults, despite persisting high concentrations of virus in urine [264]. CMV infection *in utero* leads to detectable CMV-specific $CD8^+$ T-cells as early as 28 weeks gestation, and CMV-specific $CD8^+$ T-cells from congenitally infected infants produce cytokines in response to antigen and can lyse target cells loaded with CMV peptide [266]. Despite a seemingly functional anti-CMV $CD8^+$ T-cell response in the 28-week old fetus, symptomatic CMV disease was apparent [266], suggesting that $CD8^+$ T-cell responses alone do not explain the different presentations of symptomatic CMV disease vs. asymptomatic infection. Notably, the functional responses measured in this study represent recall responses on secondary antigenic

stimulation, and would not measure relative defects in primary induction of $CD8^+$ responses in newborns and fetuses relative to adults.

Regulatory T-cells (Tregs): Regulatory T-cells (Tregs) are a population of $CD25^+$ $CD4^+$ T-cells involved in establishing and maintaining immunologic tolerance [270]. During infection, these cells may function to limit associated tissue damage [271]. This has been shown in a mouse model of HSV eye infection, where depletion of Tregs led to significant worsening of stromal keratitis, both by minimizing induction of HSV-specific $CD4^+$ T-cells and by limiting the migration of $CD4^+$ T-cells to the site of infection [272]. Tregs have also been shown to attenuate HSV-specific $CD8^+$ T-cell responses in the murine footpad model of HSV-1 infection [273]. In contrast, recent studies in the murine HSV-2 vaginal challenge model show increased mucosal pathology and morbidity in mice depleted of Tregs during the acute phase of infection [274], suggesting that the influence of Tregs may depend on the site of initial infection.

Newborn humans and mice appear to have Tregs in the same proportions as adults. T-cells with a Treg phenotype ($CD4^+CD25^+$) are detected in the thymus of a human fetus as early as 13 weeks gestation, and extrathymic $CD4^+CD25^+$ cells are detected after 14 weeks gestation [275]. The overall percentage of Tregs in newborn humans is comparable to that of adults, and consists of between about 3 and 7% of the total $CD4^+$ T-cell population [276]. In mice, Tregs comprise between 5 and 10% of the $CD4^+$ population; unlike humans, murine Tregs are not detected in the periphery before day 3 of life [275]. Peripheral lymphoid Tregs reach adult levels in mice by about day 7 of life [277].

A subpopulation of human Tregs with a naïve surface phenotype has recently been described which is less susceptible to CD95L (Fas ligand)-mediated apoptosis [276]. These cells constitute a minority of the Treg population in adults and appear to decrease in frequency with increasing age. In cord blood, almost all Tregs belong to this naïve apoptosis-resistant subpopulation. This suggests the possibility that Tregs in newborns may dampen the acute response to infection more effectively than adults, a potentially detrimental effect in some infectious settings.

The attenuated HSV-specific $CD4^+$ and $CD8^+$ T-cell responses observed in neonatal mice may be related to Tregs [277]. Consistent with prior studies in adult mice [273], HSV-specific IFN-γ production by T-cells is enhanced in both neonatal and adult mice depleted of Tregs before infection. However, in the absence of Tregs the expansion, activation, and cytotoxicity of HSV-specific $CD8^+$ T-cells four days after infection is enhanced only in neonatal mice. Treg depletion also leads to reduced HSV titers in draining lymph nodes and brain in neonates, suggesting that Treg-mediated suppression of the antiviral response may contribute to the enhanced virulence of this virus in newborns [277]. However, a separate study in adult mice showed increased morbidity and mortality in association with increased viral titers with ablation of Tregs during the acute phase of genital HSV-2 infection [274]. Although higher levels of IFN-α and IFN-γ were measured in the draining lymph nodes of Treg-deficient mice, levels of pro-inflammatory cytokines were lower in the mucosa, and corresponded to a decrease in the inflammatory infiltrate, suggesting a role for Tregs in coordinating cell trafficking during acute infection [274].

Regulatory T-cell suppression of anti-CMV responses has also been described [278]. Depletion of Tregs from adult human PBMC led to increased IFN-γ production by anti-CMV $CD8^+$ T-cells *ex vivo*, an effect which was reversed by adding back the depleted Tregs. Specific relevance of this finding to newborn or fetal CMV responses has not been demonstrated, but it may be speculated that the relative absence of Tregs in early gestation may contribute to immunopathology associated with congenital infection.

Summary—The cellular immune response of the newborn to viral infection appears to be a complex balance of various effector cells, antigenic load, and perhaps other factors (Table 3). Overall, newborns infected with HSV appear to demonstrate attenuated cellular immune responses, with both proliferation and cytokine production affected. CMV infection may also lead to some attenuation in $CD4^+$ responses in young children, though no obvious differences in $CD8^+$ T-cell responses have not been found between newborns, young children, and adults after CMV infection. The influence of Tregs on newborn responses to either HSV or CMV infection is only beginning to be understood, but immunopathology in the fetus and newborn may be influenced by the presence of Tregs.

Conclusions and future directions

The newborn display both quantitative and functional differences to older children and adult in their immune response to HSV and CMV. These differences appear in all arms of the immune response. Some but not all newborn responses to herpesviruses are attenuated or delayed, resulting in impaired induction of protective adaptive responses and memory (e.g. HSV $CD8^+$ T-cell responses). Other neonatal responses are heightened (e.g. CNS responses to TLR2, or Treg responses), resulting in greater immunopathology. Differences between the newborn response to HSV and CMV to the immunocompetent and between each virus provide important lessons about the requirements for protective immunity to both viruses and about the immunobiology of HSV and CMV.

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Table 1

Factors influencing fetal HSV or CMV infection

	HSV	CMV
Mechanical barriers	Generally an ascending infection [42,43] Transit may be limited by anatomic barriers (cervical plug; fetal membranes) and antimicrobial peptides [41]	Generally a transplacental infection [55]
Site of latency	Resides in neurons (dorsal root ganglia); may not have access to uterine structures after reactivation	May reactivate from white blood cells in uterine tissue [45]
Effect of maternal antibody	More relevant to neonatal disease (discussed below)	Neonatal Fc receptor may facilitate transplacental transmission, especially in presence of low-avidity maternal antibody [63]
Presence of viral receptors	Not known to influence HSV infection of fetus	Spatial regulation of putative CMV receptors may influence infection [69]
Viral factors	Latency is limited to neurons, which may influence likelihood of transplacental spread	Infection may influence placental cell structure and function [64].

Table 2

Influence of innate immune responses on relative susceptibility of newborns to HSV or CMV infection

	HSV	**CMV**
Toll-like receptors		
TLR3	*Ex vivo* production of IFN-α in response to HSV is diminished in newborn PBMCs relative to adults [119]	
	Poly(I:C) stimulation of cord blood mDCs induces lower cytokine responses than adults [117]	
TLR2	$TLR2^{-/-}$ mice less susceptible than wild-type to mortality after HSV-1 infection, with difference more pronounced in neonates than adults [143]	Inflammatory response to CMV in human placental cells *in vitro* depends on TLR2 [156]
TLR9	Cord blood pDCs stimulated with HSV-1 or CMV produce less IFN-α than adults [162]	
Pro-inflammatory cytokines	IL-6 and IL-8 production increased in newborn PBMCs exposed to HSV relative to adults [145], but IL-6 and TNF-α are reduced in newborn murine skin (Jones, C.A., unpublished observations) IFN-α production by neonatal PBMCs is lower after stimulation with HSV than adult PBMCs [119]	Type I IFNs are produced in lower amounts in newborn mice than adults after intracranial injection [189]
Dendritic cells	Maturation of neonatal murine DCs infected with HSV is impaired more than in adults [209], and migration to draining lymph nodes is slower (Jones, C.A., unpublished observations)	

Table 3

Influence of adaptive immune responses on relative susceptibility of newborns to HSV or CMV infection

	HSV	**CMV**
Humoral immunity	Circulating antibodies may limit viral dissemination [244,245]	
Cellular immunity	Overall diminished proliferation and IFN-γ production of newborn PBMCs relative to adults in response to HSV antigen [244,262]	Cord blood PBMCs after congenital infection can function comparably to adult cells [264–266]
$CD4^+$ T-cells	Paucity of T_H1 and T_H2 cytokines after HSV infection in neonatal mice relative to adults [263]	Lower IFN-γ and IL-2 production by $CD4^+$ T-cells in response to CMV antigen in young children relative to adults [265]. Lower expression of CD154 (CD40 ligand) in CMV-specific $CD4^+$ T-cells from young children compared with adult cells [265]
$CD8^+$ T-cells	$CD8^+$ T-cell response in draining lymph nodes is delayed in newborn mice infected with HSV compared with adults, with a lower peak activity [269]	Young children have identical frequencies of CMV-specific $CD8^+$ T-cells and detection of intracellular IFN-γ perforin as adults [264]
Tregs	Expansion, activation, and cytotoxicity of HSV-specific $CD8^+$ T-cells in the absence of Tregs is enhanced in neonatal but not adult mice [277].	