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REVIEW ARTICLE

A perfect storm: fetal inflammation and the developing immune system

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Histologic chorioamnionitis is an inflammatory disorder of the placenta that commonly precedes preterm delivery. Preterm birth related to chorioamnionitis and fetal inflammation has been associated with a risk for serious inflammatory complications in infancy. In addition, preterm infants exposed to chorioamnionitis may be more susceptible to infection in the neonatal intensive care unit and possibly later in life. A significant body of work has established an association between chorioamnionitis and inflammatory processes. However, the potential consequences of this inflammation on postnatal immunity are less understood. In this review, we will discuss current knowledge regarding the effects of fetal exposure to inflammation on postnatal immune responses.

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INTRODUCTION

The diagnosis of suspected clinical chorioamnionitis is based on non-specific symptoms, such as maternal fever, leukocytosis, abdominal or uterine tenderness, or fetal tachycardia.[1] However, the "gold standard" for confirmation of this diagnosis rests on placental evidence of acute histological chorioamnionitis (HCA), represented by the infiltration of inflammatory neutrophils in maternal or fetal placental tissues.[2] A more updated but still controversial definition of chorioamnionitis, also referred to as intrauterine inflammation, infection, or both ("Triple I"), incorporates both clinical and histologic criteria.[3] While clinical chorioamnionitis is commonly accompanied by HCA,[4] the reverse situation may not be true. In fact, most cases of HCA occur without clinical symptoms in the mother or fetus and thus present "silently."[5,6] Despite the lack of clinical expression, however, asymptomatic placental inflammation is not innocuous even in the absence of infection.[7] A diagnosis of HCA often precedes the delivery of extremely preterm infants[5] and, like clinical chorioamnionitis, is associated with early-onset infection.[8] Conversely, HCA was correlated with a decreased risk of late-onset neonatal infection with coagulase-negative staphylococci.[9] HCA has also been closely linked to the pathogenesis of serious postnatal inflammatory disorders, including bronchopulmonary dysplasia, brain injury, retinopathy of prematurity, and necrotizing enterocolitis.[10–13] Preterm infants born to mothers with clinically suspected chorioamnionitis are identified as being at higher risk for infection and are typically screened.[14] In contrast, in the absence of maternal symptoms, the possibility that a preterm infant has been exposed to HCA and a consideration of its inherent inflammatory and infectious risks may not be addressed in a timely fashion or even at all. This is particularly true given that a diagnosis of HCA rests on microscopic examination of the delivered placenta, and resulting information may not be available for days to weeks after birth.

A variety of approaches to identify gestations affected by HCA have been studied. The expression patterns of biological markers in amniotic fluid and cord blood, such as interleukin-6 and C-reactive protein, have been assessed for their predictive value in HCA; however, sensitivity and specificity of these markers have not been consistent.[15–17] Clinical prediction rules for HCA and funisitis have also been developed in order to identify newborns exposed to antenatal inflammation.[18] The targeted clinical variables included the absence of pre-eclampsia, normal intrauterine growth, maternal or fetal evidence of clinical chorioamnionitis, prolonged premature rupture of membranes (PPROM), and vaginal delivery. Although these methods have shown clinical promise, to date none have been uniformly successful in identifying gestations with HCA.

The inflammatory complications associated with HCA have been well described.[13,19–24] Less appreciated is that affected preterm infants also may be at risk for immune consequences in addition to or in combination with the adverse effects of HCA-mediated inflammation.[25,26] Increasing evidence supports the concept that the ensuing neonatal immune dysfunction reflects the effects of inflammation on immune programming during critical developmental "windows."[26] The goals of the present review article are to summarize the following: (1) The effects of inflammation during pregnancy on the reconfiguration of neonatal inflammatory and immune responses; and (2) The implications of intrauterine inflammatory exposure for immunity in the neonatal period and beyond. Understanding how in utero inflammation programs the postnatal immune response may reveal novel approaches to reduce inflammatory injury and the risk for infection in preterm infants.

EFFECTS OF ANTENATAL INFLAMMATION ON NEONATAL IMMUNITY

Inflammation and immunity

Inflammatory exposure during intrauterine life is a pathologic force that can drive alterations of postnatal innate and adaptive

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immunity (Fig. 1). A growing body of data implicates myriad environmental exposures during pregnancy, many associated with inflammation, on subsequent immunity (reviewed in ref. [25]). Recent evidence of a stereotypic developmental pattern of converging immune responses in preterm and term infants in the first 3 months of life, but divergent responses in infants with inflammatory exposure, additionally credits the role of intrauterine exposure at critical developmental windows in shaping immunity.[26]

Studies in humans and in animal models have begun to define how inflammatory exposure can shape immune function in fetuses and in the newborn period; these are summarized in several recent reviews.[27,28] Acute HCA associated with fetal inflammation is a risk factor for numerous adverse neonatal outcomes.[13,19–24] Inflammatory injury related to HCA has been observed in both extremely preterm infants as well as in late preterm infants delivered after PPROM.[29] However, HCA at the earliest gestations may more heavily influence neonatal immune responses, such as increased T helper type 17 (Th17) frequencies.[30] This enhanced effect in very preterm newborns likely reflects the age-dependent "waves" of immune cell populations with inflammatory or regulatory function that are generated in the developing fetus.[31]

Immune priming and HCA

In utero "priming" or activation of the fetal immune system at critical developmental time points can lead to chronic inflammatory disorders as well as increased vulnerability to infection after birth.[25] Maternal infections with chronic inflammation, such as human immunodeficiency virus (HIV) or malaria, during pregnancy were associated with fetal inflammation and alterations in infant B cell responses.[32] Infants born to mothers with allergic disease had lower frequencies of T regulatory (Treg) cells, which in turn were impaired in their capacity to suppress effector T cells, particularly Th2 cells.[33] This latter finding may be of particular relevance to exposed infants and future risk for asthma given its close association with Th2 polarization.[34] Furthermore, even the low-grade systemic inflammation associated with maternal obesity was shown to induce placental and fetal inflammation.[35]

Emerging evidence also points to a critical role of activated fetal cells in driving intrauterine responses during chorioamnionitis. Gomez-Lopez et al. utilized DNA fingerprinting to show that predominance of inflammatory fetal neutrophils in the amniotic fluid of gestations with chorioamnionitis was highly associated with the delivery of extremely preterm neonates.[36] Increased neonatal T cell activation has also been associated with preterm delivery.[37] Frascoli et al. observed that activation of the fetal adaptive immune system suppressed maternal–fetal tolerance in the context of preterm labor.[38] In that study, fetal blood showed early maturation of dendritic cells and enhanced maternal microchimerism in preterm relative to term gestations. In addition, preterm (but not term) fetal T cells were alloreactive to maternal antigens, and maternal antigen-specific stimulation induced the proliferation of fetal Th1-type cells. Furthermore, the cytokines (interferon-γ (IFNγ) or tumor necrosis factor-α) released by proliferating T cells directly increased myometrial contractility in an in vitro assay, suggesting a directive role of activated fetal T cells in preterm labor. Although naive T cells typically predominate in fetuses, high frequencies of memory (CD4+CD45+RO+RA−) T cells have been observed in association with preterm labor.[37] This finding may be important given differing gene expression patterns and function in naive vs. memory T cells.[39]

The inflammatory processes induced by HCA also contribute to fetal immune activation. In a recent transcriptomic study, preterm infants exposed to HCA exhibited gene expression signatures indicative of immune priming.[40] The most frequently upregulated genes in these neonates were associated with activation of innate and adaptive immune pathways. Notably, the microRNA, MiR-155, was shown to be a top upstream regulator. MiR-155 is a master modulator of inflammatory and immune responses, and its elevated expression in immune cells has been associated with chronic inflammatory states, including atopic dermatitis, multiple sclerosis, and rheumatoid arthritis (reviewed in ref. [41]). Pertinently, iR-155, which is also expressed in activated CD4+ T cells, can promote pathogenic Th17-biased responses.[42]

Evidence of immune priming was also observed in a murine model of lipopolysaccharide (LPS)-induced antenatal inflammation followed by a postnatal "second hit" immune challenge.[43] In pups exposed to antenatal inflammation, infection with Sendai virus (the murine counterpart to the respiratory syncytial virus (RSV) that causes bronchiolitis in human infants) triggered strong inflammatory responses not only in the lungs, the primary site of infection, but also in distal organs, such as the liver. This exaggerated correlation was not witnessed in infected control pups without antenatal LPS exposure. In addition, an inductive effect of maternal inflammation on lung CD4 T helper cell populations with a pro-inflammatory Th1 and Th17 phenotypes was most pronounced in exposed weanling pups relative to neonates. These findings suggested that the processes initiated in utero not only persisted but also were possibly amplified beyond the neonatal period. Interestingly, a similar enhancement of lung Th17 cells was observed following secondary RSV challenge in adult mice that had survived severe sepsis.[44]

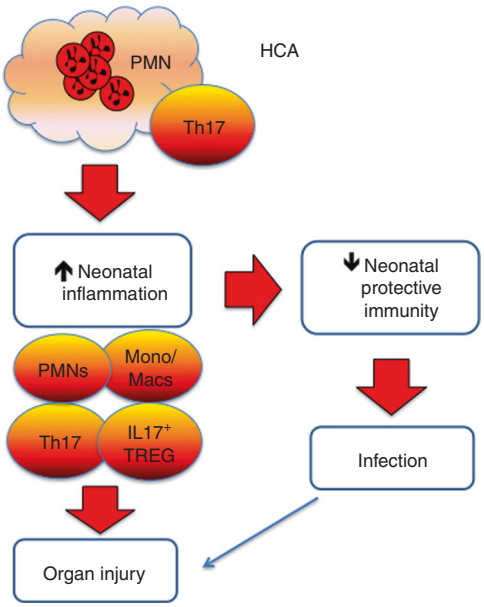

Fig. 1 Potential effects of HCA on neonatal inflammatory and immune responses. Studies in humans and in animal models have linked HCA, a neutrophil (PMN)-driven placental disorder associated with increased Th17 responses, and exaggerated inflammatory responses of both innate and adaptive immune cells. Neutrophil (PMN) production and activation may be increased, along with the release of inflammatory cytokines and chemokines that promote PMN infiltration and injury to major organs. Experimental fetal inflammation can induce functional maturation and activation of monocytes (Mono) and macrophages (Macs) that can also heighten inflammatory responses. Fetal inflammation enhances the generation of inflammatory Th17 cells and IL-17+ Treg cells; while IL-17 is important to host protection, high levels can induce organ injury, particularly in the brain. Exaggerated inflammatory responses may lead to suppression of protective immune responses, which increase risk for infection. Neonatal infection in the context of HCA exposure has also been shown to increase risk for organ injury and has been linked to bronchopulmonary dysplasia

Inflammatory innate immune responses in HCA

A number of studies have shown that experimentally induced antenatal inflammation leads to exaggerated inflammatory immune responses in exposed offspring. In ex vivo studies of preterm fetal sheep, experimental chorioamnionitis promoted the functional maturation of lung monocytes and hastened their capacity to produce inflammatory cytokines in response to stimulation.[45] Preterm piglets born after several doses of intra-amniotic LPS had increased systemic and organ-specific (gut and lung) inflammatory responses at birth.[46] In a murine model of antenatal inflammation, neonatal and weanling offspring of LPS-treated dams showed increased basal innate immune responses in the lungs and livers that were amplified following a "second hit" viral infection.[43]

The fetal inflammatory responses induced by HCA have also been shown to persist in newborn infants as systemic inflammation, much of it driven by neutrophils. As part of the ELGAN study, Chen et al. showed that the elevated levels of key neutrophil-associated inflammatory proteins (including myeloperoxidase, interleukin (IL)-1β, IL-8, intercellular adhesion molecule-3 and matrix metalloproteinase-9) in the cord blood of preterm infants born with funisitis (inflammation of cord blood vessels consistent with the fetal inflammatory response syndrome (FIRS)) remained high on postnatal day 7.[24] Autopsies of human fetuses and newborn infants who died after severe chorioamnionitis also showed amplified neutrophil production (myelopoiesis) in hematopoietic organs.[47,48] These observations are consistent with the excessive neutrophil responses associated with this perinatal condition[36,49–51] as well as the neutrophil-driven inflammatory responses in neonatal lungs and other organs.[52,53] Similar observations of neutrophil-driven inflammation have been observed in animal models. Antenatal inflammation was shown to promote neutrophil recruitment and the infiltration of organs, such as the lungs and brain.[43,54,55] High expression levels of inflammatory cytokines, including IL-1β, IL-6, IL-8, and IL-17, in the blood, thymi, lungs, and/or intestinal tracts of fetal sheep, macaques, and piglets animals following experimental chorioamnionitis have been reported.[46,56–58] In addition, altered DNA methylation profiles have been observed in placentas with HCA, reflecting activation of innate immunity and neutrophil increases.[59]

Antenatal fetal exposure has also been shown to induce inflammatory responses in the liver. In sheep studies of liver homeostasis and metabolism after LPS-induced chorioamnionitis, Vlassaks et al. found increased hepatic T lymphocytes and apoptotic hepatocytes in term newborns and increased liver triglycerides and cholesterol levels at 7 weeks of life, indicating long-lasting postnatal effects on lipid metabolism.[60] Endotoxin-induced chorioamnionitis also caused hepatic damage associated with disturbed lipid and glucose metabolism, reduced antioxidant capacity, and elevated liver enzymes.[61] The adverse hepatic effects of fetal inflammation may have specific relevance to neonatal immunity, given the increasingly appreciated role of the liver in directing immune function.[62]

Inflammatory adaptive immune responses after HCA

T helper cell subsets belong to the adaptive arm of the immune system and can promote or suppress inflammatory responses. In addition to the effects of fetal inflammation on innate immunity, recent studies have identified the robust involvement of pro-inflammatory T helper cell lymphocyte subsets, such as Th17 cells, in fetuses or preterm infants with antenatal inflammation. Th17 cells characteristically function to protect the host against extracellular pathogens.[63–65] However, under certain inflammatory conditions, Th17 cells may become pathogenic and promote tissue injury.[66] Th17 cells release the canonical cytokine, IL-17, which is also produced by other immune cells such as γδ T cells and pro-inflammatory Treg cells.[67] IL-17 plays a critical role in processes involved in FIRS associated with HCA.[58] The developing brain is particularly sensitive to inflammatory injury, and exposure to IL-17 at critical "windows" of immune development can induce microglial activation and white matter injury (reviewed in ref. [68]). Furthermore, in addition to directly inducing tissue injury, Th17 cells can amplify inflammatory responses through cross-talk with neutrophils.[69]

While Th17 cells play an important biological role in normal pregnancy,[70] increased frequencies of pathogenic Th17 cells have been observed in placentas of women with recurrent miscarriages[71] and in gestations affected by chorioamnionitis.[72] Higher circulating Th17 frequencies in mothers or in the cord blood of babies of preterm gestations with HCA have also been reported.[30,73] The exact mechanism(s) that promote Th17 responses in the context of HCA remain enigmatic. However, the expression levels of several cytokines that are critical to the propagation of Th17 cells from naive CD4 cells, including IL-1β and IL-6,[74] are also increased in the amniotic fluid in HCA.[75,76] The finding that inflammatory neutrophils promote in vitro propagation of Th17 cells[77] suggests their contribution to an intrauterine cytokine milieu that also modulates Th17 responses in HCA, as observed in the context of chronic inflammatory conditions, such as rheumatoid arthritis.[78]

In a recent human study, cord blood from preterm and term infants with HCA had increased frequencies of Th17 cells relative to unaffected controls.[30] Th17 cells were highest in the cord blood of extremely preterm infants, who also exhibited increased T cells with an effector memory phenotype associated with Th17-type responses.[79] In addition, the elevated circulating Th17 frequencies observed at birth in preterm neonates exposed to chorioamnionitis persisted in the first month of life.[73] Increased Th17-type responses have been observed in the cord blood of human infants following both acute and chronic HCA[72] and in animal models in the context of antenatal inflammation. Fetal macaques exposed to LPS-induced chorioamnionitis had increased splenic IL-17+ and IL-22+ Th17 cells,[58] while weanling murine pups exposed to LPS exhibited increased lung Th17 responses.[43]

Treg cells constitute a T helper cell subset that typically functions to suppress activated cells and inflammatory responses, including those mediated by Th17 cells.[80,81] Chorioamnionitis has been variably associated with decreased Treg cell frequencies or reduced Treg-suppressor function.[82] Fetal rhesus monkeys and sheep exposed to experimental chorioamnionitis had an increased ratio of IL-17-producing cells to Treg cells in lymphoid organs.[83] Exposure was also associated with decreased frequencies of circulating Treg cells in extremely preterm human neonates and in fetal macaques.[30,58] However, the majority of Treg cells in these two studies also co-expressed the canonical Th17 transcription factor, RORγt, and/or IL-17, consistent with a pro-inflammatory rather than a regulatory phenotype.[84,85] Pertinently, IL-17+ Treg cells can serve as a major source of IL-17 during inflammation.[84]

The enhanced Th17-type responses observed in conjunction with antenatal inflammation have been linked to inflammatory injury in the lungs or brain. Elevated frequencies of IL-17-producing cells in fetal rhesus monkeys with chorioamnionitis were associated with lung inflammation in neonates.[83] When LPS-induced antenatal inflammation was combined with neonatal hypoxic–ischemic brain injury in a rat pup model, Th17-like lymphocytes migrated to the brain to direct neuroinflammatory responses.[86] Th17 cells appear to be the major cell group mediating this inflammatory IL-17 effect; while γδ t cells also produce IL-17,[87] experimental HCA did not measurably alter this lymphocyte population in exposed lambs.[88]

Other lymphocyte subsets may have the capacity to contribute to neonatal inflammatory responses in HCA that are not mediated by IL-17. A higher proportion of Th1 cells were determined in the umbilical cord blood of human neonates with clinical evidence of perinatal infection.[89] A recently described subset of lymphocytes

unique to cord blood produces IL-8/C-X-C chemokine motif ligand 8 and can activate neutrophils and γδ t cells,[90] although whether and how HCA influences these lymphocytes is not clear.

Immune suppression and HCA

In contrast to the hyper-inflammatory responses associated with HCA exposure, protective immune responses may be suppressed. Immune-suppressive mechanisms in chorioamnionitis may be selectively quantitative. Human fetuses and neonates exposed to chorioamnionitis have been shown to exhibit both thymic involution and depletion of splenic T cells.[91,92] Studies in fetal sheep affected by chorioamnionitis found reductions in CD8+ but not in CD4+ T cells in thymic cell populations.[93]

Intrauterine inflammatory exposure may also lead to qualitative alterations in neonatal innate or adaptive immune function. A relationship between an inflammatory antenatal environment and immune suppression is suggested by the enhanced HIV positivity observed in human infants born to HIV-affected mothers in the context of chorioamnionitis,[94] possibly due to activated fetal lymphocytes.[95] A recent study also showed suppressed transcriptional responses to *Staphyloccoccus epidermidis* in ex vivo monocytes from preterm human neonates with chorioamnionitis.[96] Studies in animal models are supportive of this premise: Repetitive intrauterine LPS exposure in sheep induced "immune paralysis" of ex vivo fetal and neonatal monocytes following stimulation with LPS or other Toll-like receptor ligands.[45,97] Similarly, chronic, but not acute, intra-amniotic infection with *Ureaplasma parvum* resulted in suppressed "second hit" LPS-induced cytokine responses in the fetal lung.[98,99] This evidence further supports the idea that prenatal exposure to HCA-mediated inflammation, particularly if long-standing, can alter postnatal immune response patterns. Pertinently, septic human neonates have been observed to exhibit early hyper-inflammatory responses followed by suppressed immune responses,[100] a pattern reminiscent of that observed in infants exposed to HCA. Similarly, Azizia et al. found a correlation between prematurity, neonatal sepsis, and reduced monocyte major histocompatibility complex class II expression associated with immune paralysis in HCA-exposed gestations, with an increased risk for sepsis and organ dysfunction.[101]

Potential mechanisms of immune suppression in HCA

The immune system in preterm infants is developmentally restricted in its capacity to protect the host against infection.[102] The added burden of intrauterine inflammatory exposure during sensitive developmental "windows" to already impaired immune function also remain incompletely understood but may involve developmentally regulated epigenetic processes.[103] In studies of short-term antenatal LPS exposure in preterm sheep, the role of timing rather than the specific inflammatory trigger was found to have a greater impact on abnormal neurological findings in the fetal brain.[104] However, the mechanisms involved in the inflammation-induced immune suppression of infants exposed to HCA, like the immune dysfunction associated with neonatal sepsis,[100] remain incompletely understood.[105]

A variety of quantitative and qualitative alterations of immune function that are biologically prevalent in preterm infants can contribute to processes that suppress immunity[31,106] (Fig. 2). The characteristic limitations of neutrophil production and storage that are typical in preterm infants can lead to rapid depletion and severe neutropenia during periods of increased utilization, such as sepsis.[107] In addition, neonatal neutrophils and monocytes exhibit intrinsic dysfunction, including hyporesponsiveness to stimulation and impaired antimicrobial capacity[108,109] that may be additionally affected by inflammation-induced immune paralysis. HCA can induce excessive fetal neutrophil production (granulopoiesis), suggesting a fetal capacity to overcome or circumvent developmental restrictions under inflammatory conditions.[110] However, the functionality of these newly minted neutrophils may also be impaired. Inflammation can lead to hypofunctional T cells through a process that downregulates the T cell receptor zeta-chain,[111]

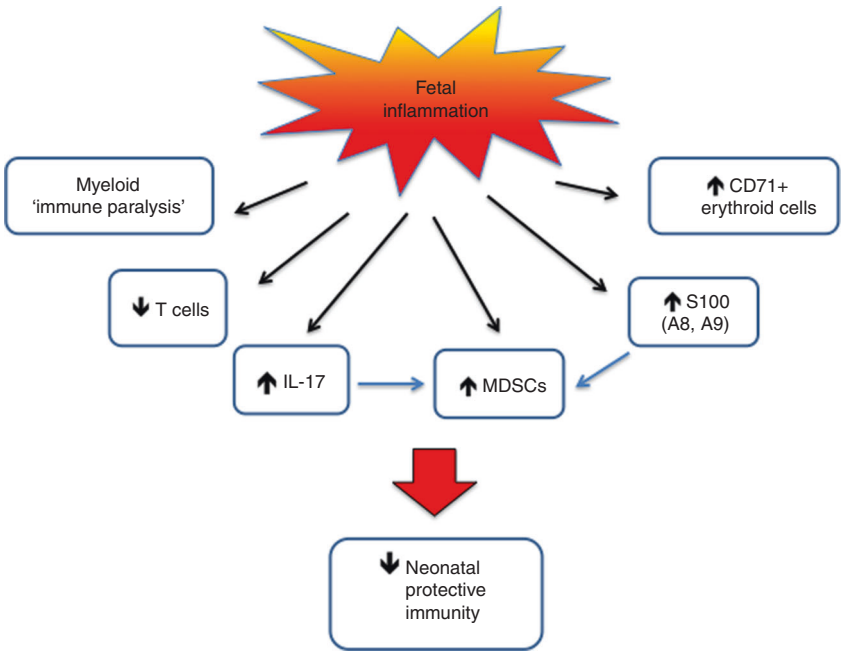

Fig. 2 Potential mechanisms of suppressed protective immunity in neonates exposed to fetal inflammation associated with HCA. Experimental HCA has been associated with "immune paralysis" as suggested by decreased LPS responsiveness in fetal sheep monocytes. HCA has been variably associated with quantitative and qualitative defects in T cells. Conversely, increases in Th17 and inflammatory Treg cells promote IL-17 release. While IL-17 provides immune-protective function, it can also promote the generation of myeloid-derived suppressor cells (MDSCs), which adversely affect protective immunity. The increased expression of S100 proteins, particularly S100A8 and S100A9, may promote host protection; however, high levels can increase MDSC generation. Recent evidence also indicates an immunosuppressive role of CD71+ erythroid cells, which could potentially be increased with HCA

although whether this functions as a suppressive mechanism in the context of HCA is unknown. Conversely, while neonatal immune cells are also at a developmental disadvantage in terms of generating protective cytokines, such as IFNγ, neonatal Th1 cell frequencies may be increased following HCA exposure.[112]

Cells with regulatory function may serve to further suppress immune function in newborns exposed to HCA (Fig. 2). Granulocytic myeloid-derived suppressor cells (Gr-MDSCs), an immature neutrophil subset with high frequencies in neonates, suppress T cell function.[113,114] This action may occur through the reduction of L-arginine levels,[115] which are biologically low in preterm infants.[116] Pertinently, increased expression of arginase 1 and subsequent depletion of L-arginine were observed in exposed offspring in a rat model of LPS-induced chorioamnionitis.[117] MDSCs are also important negative regulators of inflammatory responses.[118,119] Elevated circulating frequencies of Gr-MDSCs have been reported in extremely preterm infants in association with clinical inflammation, though not specifically HCA.[120] Importantly, these MDSCs persisted for several months beyond the immediate neonatal period, suggesting an immunosuppressive role in later infancy. Neonatal inflammatory neutrophils and monocytes also release the alarmins, S100A8 and S100A9, which may suppress hyper-inflammatory responses through the expansion of MDSCs.[121,122] Pertinently, increased S100 protein expression levels in amniotic fluid have been observed in gestations with HCA.[123]

Lymphocytes with intrinsic suppressive function can also inhibit immune responses in preterm infants. Treg cells are critical to the suppression of T cell responses to self and maternal antigens that is necessary for maternal–fetal tolerance.[124,125] Although Treg cells in preterm infants with HCA may exhibit a pro-inflammatory (Th17-like) phenotype,[30] conversely their release of IL-17 could attract MDSCs to mediate immune suppression.[126] Regulatory B cells, another type of immune cell, can modulate neonatal inflammatory responses[127] and promote Th2 skewing in neonatal mice through suppressive actions on dendritic cells.[128]

Recent evidence also points to a role of a unique subset of CD71+ erythroid cells in modulating myeloid and T cell responses.[129] Pertinently, these regulatory erythroid cells are found in high numbers in preterm but not in term neonates. CD71+ cells were shown to suppress protective immune responses to pertussis infection in neonatal mice, in part through actions mediated by arginase and the expression of programmed death ligand-1.[130]

Steroid-associated effects on immune responses in HCA

While current treatment guidelines for chorioamnionitis are institutionally varied, antenatal steroids (such as betamethasone) are commonly administered for preterm labor. A recent meta-analysis showed that steroid administration in the setting of HCA was associated with reduced mortality and incidence of respiratory distress, patent ductus arteriosus, intraventricular hemorrhage (IVH), and severe IVH; in the setting of clinical chorioamnionitis, steroid administration reduced severe IVH and periventricular leukomalacia.[13] Although several studies suggest that antenatal steroids can dampen the inflammatory cascade, their effects on fetal inflammation are not well defined. Evidence of anti-inflammatory effects of steroid administration includes the inhibition of intrauterine transforming growth factor-β signaling associated with fetal lung inflammation and the partial prevention of the structural lung changes induced by LPS exposure.[131,132]

The antenatal timing of steroid administration may also influence inflammatory responses. Kuypers et al. showed that, while steroid administration prior to intrauterine LPS exposure reduced the adverse effects of inflammation on the brain in fetal sheep, conversely steroids aggravated inflammatory changes in the brain and thymus in the context of pre-existing inflammation.[56,133] These observations suggest that, in the presence of chorioamnionitis, steroids could potentially amplify fetal injury in an organ-specific manner. In studies of fetal sheep exposed to intra-amniotic endotoxin and subsequently treated with steroids, inflammatory responses in ex vivo monocytes were initially suppressed but were followed by a later activation, possibly the result of steroid-induced functional maturation.[134]

SUMMARY

HCA is a common disorder that is tightly linked to preterm delivery and dysregulated immune function. Inroads are being made toward better defining the immune effects of antenatal inflammatory exposure on the fetus and newborn, which includes a pattern of hyper-inflammation combined with immune suppression. However, much remains to be learned regarding the underlying mechanisms so that potential therapeutic targets can be identified.

Perinatal inflammation has clear implications for human health. Mounting evidence points to a negative impact of early inflammatory exposure of any origin on the developing immune program.[135,136] Chorioamnionitis has been identified as a contributing factor in childhood asthma,[137,138] possibly through a mechanism involving Th2 skewing.[139] However, much remains to be learned in this regard. Numerous factors aside from microbial exposure have been shown to induce systemic maternal inflammation and/or chorioamnionitis, including nutritional and psychosocial factors (reviewed in ref. [135]). Of great concern are the observations linking perinatal inflammation from various causes with immune dysfunction and abnormal stress responses, not only in the immediate postnatal period but also possibly throughout life or even into the next generation.[140] Thus the importance of advancing knowledge of perinatal inflammation and its causes cannot be overstated.

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Substantial contribution to conception and design and drafting the article or revising it critically for important intellectual content: both the authors. Final approval of the version to be published: J.K.

ADDITIONAL INFORMATION

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