

Placental Regulation of Maternal-Fetal Interactions and Brain Development

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ABSTRACT: A variety prenatal insults are associated with the incidence of neurodevelopmental disorders such as schizophrenia, autism and cerebral palsy. While the precise mechanisms underlying how transient gestational challenges can lead to later life dysfunctions are largely unknown, the placenta is likely to play a key role. The literal interface between maternal and fetal cells resides in the placenta, and disruptions to the maternal or intrauterine environment are necessarily conveyed to the developing embryo via the placenta. Placental cells bear the responsibility of promoting maternal tolerance of the semiallogeneic fetus and regulating selective permeability of nutrients, gases, and antibodies, while still providing physiological protection of the embryo from adversity. The placenta's critical

role in modulating immune protection and the availability of nutrients and endocrine factors to the offspring implicates its involvement in autoimmunity, growth restriction and hypoxia, all factors associated with the development of neurological complications. In this review, we summarize primary maternal-fetal interactions that occur in the placenta and describe pathways by which maternal insults can impair these processes and disrupt fetal brain development. We also review emerging evidence for placental dysfunction in the prenatal programming of neurodevelopmental disorders. © 2012 Wiley Periodicals, Inc. *Develop Neurobiol* 00: 000–000, 2012

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INTRODUCTION

A key advance in modern neurobiology is the understanding that the nervous system exhibits lifelong reciprocal interactions with the immune and endocrine systems. These interactions and their high sensitivity to environmental cues means that alterations in one domain leads to changes in another. This is evident in systemic infection, where activation of an immune response in the periphery leads to activation of vagal afferents and their projection areas in the brain, causing changes known as sickness behavior (Dantzer et al., 2008). In the other direction, during the stress response, activation of hypothalamic neurons stimu-

lates the hypothalamic-pituitary-adrenal (HPA) axis and corticosterone production (Dedovic et al., 2009). These effects of stress lead to altered peripheral immune function (Segerstrom and Miller, 2004).

Such plasticity is particularly important during embryonic development, enabling an organism to adapt to the demands of the environment in which it develops and will eventually inhabit. While this ability to reorganize regulatory systems in response to immediate environmental pressures confers an obvious adaptive advantage, it also entails a risk for adverse, long-term effects on physiological functions, particularly if the prenatal environment is discordant with the postnatal environment. That is, priming of fetal development *in utero* may lead the offspring to respond inappropriately to a postnatal environment that is different from that for which it was prepared. This is exemplified in the effect of maternal undernutrition on offspring metabolism and subsequent susceptibility to obesity (Krechowec et al., 2006). Such

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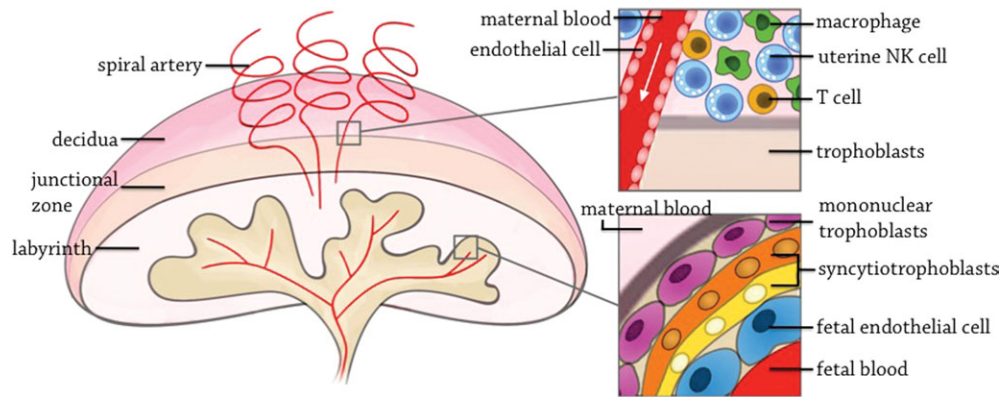


Figure 1 The maternal–fetal interface in the murine placenta. The direct interaction between maternal and fetal cells during gestation occurs in the placenta. The placenta is of dual origin, with the outer decidual layer composed almost entirely of maternal immune cells, while the underlying junctional zone and labyrinth layers (chorionic villous layer, in human) are comprised exclusively of fetally derived trophoblasts and leukocytes. Maternal immune cells and endothelial cells of the spiral arteries are juxtaposed along trophoblasts at the boundary between the decidua and junctional zone (upper right). In the labyrinth layer, intervillous spaces are lined by fetal syncytiotrophoblast cells, mononuclear trophoblast cells, and fetal endothelial cells that separate maternal from fetal blood (lower right).

findings support the concepts of “fetal programming” and the “developmental origins of health and disease,” which describe how environmental influences on early development initiate molecular responses that impact long-term predisposition for disease.

A variety of maternal and intrauterine insults are known to affect fetal neurodevelopment, but the mechanisms underlying how such transient prenatal challenges can lead to persistent postnatal dysregulation are largely unknown. It is likely that the placenta, as a key regulator of maternal–fetal interactions, plays an important role. Indeed, changes in placental shape and weight are associated with the development of diseases such as hypertension, coronary heart disease and stroke in later life (Barker et al., 1990; Warning et al., 2011). Moreover, the placenta’s central role in regulating nutrient transport, endocrine function and immune tolerance implicates its involvement in growth restriction, hypoxia and related neurological complications (Jansson and Powell, 2007; Bale et al., 2010; Fernandez-Twinn and Ozanne, 2010). In this review, we briefly describe some of the complex, maternal–fetal interactions that occur in the placenta. We further discuss the pathways by which maternal perturbations known to alter neurodevelopment also disrupt placental physiology. We place particular focus on murine studies, from which several mechanistic insights into how placental disruptions influence offspring development have been drawn. In closing, we review emerging evidence for a placental

role in prenatal programming of neurodevelopmental disorders.

MATERNAL–FETAL INTERACTIONS IN THE PLACENTA

Far from being a passive organ, the placenta plays a critical role in orchestrating the sequence and intensity of a series of complex maternal–fetal interactions. In essence, the placenta is of dual origin, comprised of both fetally- and maternally derived cells (Fig. 1). The decidua, often referred to as the maternal compartment, forms the most superficial layer surrounding the placenta and is densely packed with maternal immune cells. Beneath this, a layer of fetally derived trophoblast cells secretes hormones and endocrine factors that support both maternal and fetal health. Finally, maternal blood, descending from decidual spiral arteries, and fetal blood, rising through the umbilical arteries, converge in the villous spaces of what is known as the labyrinth layer, in mice, or the chorionic villi, in humans. Here, maternal and fetal blood flow countercurrently and are separated by two layers of fetal trophoblast cells, the syncytiotrophoblasts and the so-called mononuclear trophoblasts, in mice, or villous cytotrophoblasts, in humans. These trophoblasts are critical for regulating the selective entrance of nutrients and oxygen into the fetal bloodstream.

Table 1 Immunological Tolerance at the Maternal-Fetal Interface: Molecular Mechanisms Initiated by Trophoblast Cells

	Mechanism	Function
Immuno-suppression via paracrine signaling	IDO secretion	Inhibit T cell responses via tryptophan depletion
	VIP secretion	Promote differentiation of regulatory T cells
	Soluble HLA-G secretion	Protect against NK-cell mediated cytotoxicity
Cell-cell interaction	FasL expression	Induce apoptosis upon ligation of Fas expressed on activated leukocytes
	Trophoblast shedding	Expose the maternal circulation to paternal antigens shed from trophoblast cells
Induction of maternal tolerance	Fetal microchimerism	Expose the maternal circulation to paternal antigens via direct trafficking of fetal cells
	Lack of surface MHCII	Elude recognition by CD4+ helper T cells
Immune evasion	Lack of HLA-A and HLA-B	Elude recognition by CD8+ cytotoxic T cells
	Expression of HLA-C, HLA-E and HLA-G	Draws decreased recognition by the immune system because these MHC isotypes exhibit low to undetectable levels of polymorphism

Immune Tolerance

The literal maternal–fetal interface resides at the decidual-trophoblast junction of the placenta and across the syncytiotrophoblast cells that form the boundary between maternal and fetal blood spaces in the villous layer (Fig. 1). It was recognized early on that the close contact between maternal and fetal cells at this interface represents an immunological paradox (Medawar, 1953); that is, how can trophoblast cells, which express paternal alloantigens, live harmoniously with maternal leukocytes that are developmentally educated to react against nonself antigens? Of particular concern is the reactivity of a unique population of uterine natural killer (uNK) cells, which constitutes ~70% of all decidual leukocytes (Bulmer et al., 2010) and displays cytotoxicity *in vitro*. Maternal macrophages, which form about 20% of all decidual leukocytes, along with maternal T cells and dendritic cells, retain their effector functions and reside closely with fetal trophoblasts (Scaife et al., 2003). Furthermore, that Rhesus disease involves maternal antibody production against the offspring's paternally inherited Rh factor demonstrates that the maternal adaptive immune system is capable of reacting against fetal antigens.

On the other hand, antifetal immune responses are specifically suppressed during pregnancy (Aluvihare et al., 2004). Remarkably, pregnant mice will accept an allogeneic tumor graft if harboring offspring with matching alloantigens (Tafari et al., 1995). Furthermore, acceptance of the allograft is limited to the gestational period; after birthing, allografts are rejected. This indicates that the maternal immune system is specifically tolerized to fetal alloantigens during pregnancy.

There are several mechanisms underlying immune tolerance in the placenta, and many of these depend on crosstalk between maternal and fetal cells (Table 1). Paracrine signaling between fetal and maternal cells is critical for establishing a state of immunosuppression. Trophoblast cells secrete a variety of immunosuppressive factors and harbor surface ligands to control immune reactivity through cell–cell interactions. Shedding of trophoblast antigens and trafficking of fetal cells into the maternal circulation are believed to promote classical immune tolerance during major histocompatibility complex (MHC) restriction and maturation of maternal T cells. Of principal importance is that trophoblasts exhibit limited expression of surface MHC alloantigens as a strategic way to evade maternal immune surveillance. Similar mechanisms of host immune evasion are used by tumor cells and the human immunodeficiency virus (HIV) (Collins and Baltimore, 1999; Fruh et al., 1999).

Breaching immunological tolerance at the maternal-fetal interface can result in a number of obstetric complications (Trowsdale and Betz, 2006; Warning et al., 2011). Insufficient immunological tolerance is believed to underlie many cases of pre-eclampsia and miscarriage, which is consistent with epidemiological associations of these conditions with pre-existing autoimmune disease in the mother (Wolfberg et al., 2004; Tincani et al., 2008). A signature of altered immunological status in the placenta is infiltration of uterine and decidual leukocytes into fetal compartments. Lack of tolerance also entails maternal reactivity against paternal antigens on fetal cells, which can result in cytotoxicity, placental necrosis and maternal production of anti-fetal antibodies. Notably, maternal autoantibody production against fetal anti-

Table 2 Molecular Mechanisms Underlying Trophoblast Invasion and Spiral Artery Modification at the Maternal-Fetal Interface

	Mechanism	Function
Altered gene expression	PECAM-1 and VE-cadherin expression	Alter display of surface adhesion molecules to aid in the migration towards the decidua and to establish characteristics of endothelial cells
	Matrix metalloproteinase expression	Digest the extracellular matrix during the travel toward the myometrium
Paracrine signaling to decidual cells	HGF, EGF and LIF secretion	Factors to stimulate invasion
	TGF β , IFN γ and IL-11 secretion	Factors to limit the extent of invasion
	TNF α and TRAIL secretion	Initiate caspase activation and apoptosis of endothelial cells and stromal cells
Cell-cell interactions	Surface HLA-C and HLA-G expression	Bind to killer immunoglobulin receptors on uNK cells or LIL receptors on decidual macrophages to regulate cytokine expression

gens is involved in a number of developmental disorders, including autism (Braunschweig et al., 2008). Thus, while numerous strategic mechanisms have evolved to accommodate the coexistence of maternal and fetal cells in the placenta, insults which impact placental signaling factors and immune status can lead to deficits in immunological tolerance at the maternal–fetal interface.

Trophoblast Invasion

At the same time that maternal and fetal cells in the placenta must interact to maintain immunological tolerance, they also need to coordinate to deliver progressively more nutrients to the growing embryo. This is achieved specifically in hemachorial placentas (where chorionic cells come into direct contact with maternal blood) by specialized groups of trophoblast cells that travel into spiral arteries and initiate vascular remodeling (Moffett and Loke, 2006; Cartwright et al., 2010). Interstitial trophoblasts, which derive from villous trophoblasts, invade the decidua and spiral arteries. There, they initiate programmed cell death of existing maternal endothelial and smooth muscle cells, opening up blood flow to accommodate the needs of the developing fetus. This process effectively increases the diameter of the spiral arteries, allowing maternal blood to fill the villous spaces at an elevated rate with decreased resistance. Thus, greater levels of nutrients, growth factors and oxygen are transferred to the fetal circulation to promote healthy embryonic development.

Successful trophoblast invasion is mediated by crosstalk between the interstitial trophoblasts and the diverse cell types that they encounter on the journey toward the decidua (Table 2). These interactions result in an intricate sequence of temporally- and spa-

tially restricted changes in gene expression. For example, interactions with distinct placental cell types trigger invading trophoblast cells to change their display of surface adhesion molecules as they migrate up to the decidua, progressively acquiring characteristics of endothelial cells. Furthermore, invading trophoblasts upregulate expression of molecules that help to digest the extracellular matrix barrier. The extent of invasion is further governed by cytokine signaling between decidual cells and interstitial trophoblasts. Direct cell–cell interactions between trophoblasts and decidual leukocytes may also regulate invasion and spiral artery modification.

Modification of Spiral Arteries/Vascular Remodeling

The transformation of spiral arteries after trophoblast invasion reflects a culmination of several molecular events that effectively alter the vascular properties of the spiral arteries. The invasive trophoblasts themselves are important for inducing apoptosis of endothelial cells and stromal cells in the vasculature. Even prior to trophoblast invasion, decidual immune cells localized near the vessel walls initiate early arterial vacuolization and dilation (Hazan et al., 2010). Moreover, it is believed that the phagocytic properties uNK cells aid in the clearance of apoptosed endothelial and stromal cells surrounding the spiral arteries, making way for new endothelial-like trophoblasts to reconstitute the vasculature.

Both trophoblast invasion and vascular remodeling are intimately tied to fetal growth and development. Disruption of either process leads to altered maternal blood flow into the villous spaces and inappropriate exchange of nutrients and respiratory gases. This can be detected histologically by shallow extravillous

trophoblast invasion or over-infiltration of the decidual matrix and suboptimal vascularization. Associated changes in blood circulation and flow resistance can be conveyed by altered experimental parameters during placental perfusion. These molecular disruptions can form the mechanistic bases for fetal malnutrition, intrauterine hypoxia and altered placental weight or birth weight (Roberts et al., 2001; Redmer et al., 2004; Sibley et al., 2005; Cartwright et al., 2007). A variety of medical conditions arise from such complications, including premature birth, pre-eclampsia and intrauterine growth restriction (IUGR) (Sibley et al., 2005; Cudihy and Lee, 2009), and these conditions are further associated with a number of neurodevelopmental disorders, such as cerebral palsy and schizophrenia (Preti et al., 2000; Jarvis et al., 2006; Redline, 2006; Clarke et al., 2011; O'Callaghan et al., 2011).

PRENATAL EFFECTS ON THE PLACENTA AND NEURODEVELOPMENT

It is clear that the molecular mechanisms regulating normal placental functions are tightly intertwined, governed by both cells at the maternal–fetal interface and soluble factors in the local microenvironment. Signaling of cytokines, growth factors and hormones are central to the cross-talk between maternal and fetal cells in the placenta, dictating the gene expression changes that modulate their physiological functions. Also, the activation states of decidual immune cells can influence not only immunological tolerance at the maternal–fetal interface, but also the production of soluble factors and types of cell–cell interactions that influence trophoblast invasion and vascular remodeling. Overall, the cellular interactions underlying these processes are critical for establishing normal placental architecture, delivering sufficient oxygen and nutrients to the fetus and protecting the fetus from maternal reactivity. Thus, a proper intrauterine environment is fundamental to the success of the placenta and pregnancy in supporting healthy fetal development.

Maternal insults that disrupt the fine interplay of signaling networks at the maternal-fetal interface can alter placental capacity and complicate fetal development and behavior. Given that maternal challenges are conveyed to the fetus via the placenta, many maternal insults lead to altered intrauterine environments and consequent placental pathology. Maternal anemia, for example, is associated with altered placental angiogenesis, intrauterine hypoxia and perinatal brain injury in the offspring (Kadyrov et al., 1998;

Fowden et al., 2008). Here we discuss maternal immune activation (MIA) as a major factor known to disturb placental physiology and lead to alterations in offspring brain development with long-term consequences.

Maternal Immune Activation

While normal pregnancy involves several mechanisms to promote immunosuppression and immune evasion at the maternal–fetal interface, the placenta retains the ability to detect and respond to infection and inflammation. Placental cells express a variety of pattern recognition receptors (PRRs) that recognize unique microbe-associated molecular patterns (MAMPs) expressed extracellularly or intracellularly on microorganisms. PRRs such as mannose receptors, NOD-like receptors and Toll-like receptors (TLRs) are expressed not only on placental immune cells, but also on trophoblasts themselves (Koga and Mor, 2010). In fact, all 10 TLRs, in addition to many related coreceptors and accessory proteins, are found in the human placenta, rendering the placenta responsive to MAMPs on bacteria, viruses, parasites, and fungi.

In animal models, respiratory infection or injection of MAMPs, such as the bacterial cell wall component lipopolysaccharide (LPS) or the synthetic double-stranded RNA poly(I:C) (to mimic viral infection), into pregnant dams triggers a maternal inflammatory response that can lead to placental pathology and subsequent harm to the fetus (Koga and Mor, 2010). The precise developmental effects of MIA depend on the specific antigen used, as well as the dosage, route, and timing of administration. Early gestational injection of LPS or poly(I:C), for example, can lead to implantation failure or fetal resorption, while exposure during late gestation can induce preterm birth (Ilievski et al., 2007). Relatively low-dose LPS or poly(I:C) injection into rodents during mid-to-late-gestation yields offspring with schizophrenia- and autism-related developmental abnormalities in the absence of overt obstetric complications (Patterson, 2011). Common to these variations of MIA, however, is a consistent upregulation of proinflammatory cytokines, chemokines and reactive oxygen species in the maternal blood and placenta.

MIA induces the production of soluble proinflammatory factors that have access to placental cells via maternal blood in the spiral arteries and intervillous spaces. Moreover, MIA can alter the immune status of decidual leukocytes, including upregulation of activation markers and increased production of proin-

flammatory cytokines by uNK cells, macrophages and granulocytes (Zhang et al., 2007; Renaud and Graham, 2008; Hsiao and Patterson, 2011). Not surprisingly, these effects on uterine immune cells can lead to further disruption of immunological tolerance, cytoarchitecture, and blood circulation in the placenta. Maternal LPS injection, for instance, induces necrosis and edema of the labyrinth layer, infiltration of maternal immune cells into fetal placental tissues and decreased placental perfusion (Girard et al., 2010; Carpentier et al., 2011). LPS-mediated activation of TLR4 signal transduction also inhibits the migration of trophoblast cells (Abrahams et al., 2005), which may form the basis of observed decreases in placental circulation.

In response to maternal poly(I:C) injection, however, the placenta experiences a dramatic upregulation of proinflammatory cytokines and activation of decidual immune cells, in the absence of obvious pathophysiology (Zhang et al., 2007; Hsiao and Patterson, 2011). The maternal proinflammatory response is further relayed to fetal spongiotrophoblast and labyrinth cells, which activate JAK/STAT signaling pathways and alter expression of several genes, including those that encode important endocrine factors such as growth hormone and insulin-like growth factor 1 (IGF1) (Fatemi et al., 2011). Importantly, these effects on the placenta, as well as MIA-induced behavioral abnormalities in the offspring, are dependent on IL-6 signaling (Smith et al., 2007; Hsiao and Patterson, 2011). In addition to these changes in factors that influence fetal health, some proinflammatory cytokines, such as IL-6 and IL-1 β , can cross the placenta and enter the fetal bloodstream (Dahlgren et al., 2006; Girard et al., 2010). Thus, soluble factors produced in response to maternal insults can activate cells at the maternal–fetal interface and potentially be passively transported directly into the fetal circulation. These findings highlight the key role of the placenta in amplifying the maternal inflammatory response and potentiating detrimental effects on embryonic health. They further contribute to a growing number of MIA studies that demonstrate a critical role of cytokine signaling in triggering molecular cascades that ultimately impair fetal development.

The long-term effects of MIA on the offspring include a variety of behavioral, histological, and immunological abnormalities that relate to symptoms of human autism and schizophrenia. Adult MIA offspring exhibit deficits in prepulse inhibition, latent inhibition, open field exploration, social interaction, and vocal and olfactory communication, as well as increased anxiety and repetitive/stereotyped behavior (Malkova et al., 2012). They also exhibit enlarged

ventricles, a hallmark neuropathology of schizophrenia and a spatially restricted deficit in cerebellar Purkinje cells, a characteristic neuropathology of autism, among several other neuropathologies (Patterson, 2007). Young and adult MIA offspring also display autism-related immune dysregulation, including decreased T regulatory cells and hyper-responsive CD4⁺ T cells (Hsiao et al., 2011). Together, these effects of MIA in animal models support large epidemiological studies linking maternal viral, bacterial and parasitic infection to increased risk of schizophrenia or autism in the offspring (Patterson, 2007). Also supporting this body of work are associations between these mental illnesses and elevated cytokines in amniotic fluid and maternal serum.

THE PLACENTA IN PROGRAMMING OF NEURODEVELOPMENTAL DISORDERS

Altered placental function and the release of deleterious factors to the fetus, in response to such challenges as MIA, are important risk factors for the pathogenesis of neurodevelopmental disorders. Several maternal insults, including maternal infection and maternal malnutrition, increase susceptibility to IUGR, and all three factors are epidemiologically linked to schizophrenia, autism and cerebral palsy in the offspring (Brown and Susser, 2008; Atladottir et al., 2010; Brown and Patterson, 2011; O’Callaghan et al., 2011). Placental pathologies relating to vascular impairments, including chorionic vessel thrombi, villous edemas and vascular necrosis, are prevalent in cerebral palsy (Redline, 2006). In addition, obstetric complications are associated with increased risk for schizophrenia and can predict treatment responses in schizophrenic individuals (Alvir et al., 1999; Preti et al., 2000). Exposure to obstetric complications and immune dysregulation are similarly linked to autism susceptibility in the offspring (Limperopoulos et al., 2008; Gardener et al., 2009; Sacco et al., 2010). In one study, trophoblast inclusions were increased in placental tissue derived from births of individuals who developed autism spectrum disorder (Anderson et al., 2007). In addition, chorioamnionitis, or inflammation of the fetal placental membranes, is associated with impairments in social interaction and communication in autistic children (Limperopoulos et al., 2008).

That placental pathologies are associated with brain injury and altered behavior suggests that dysfunction at the maternal–fetal interface can contribute to the pathogenesis of neurodevelopmental disorders (Fig. 2). Whether placental impairments can directly

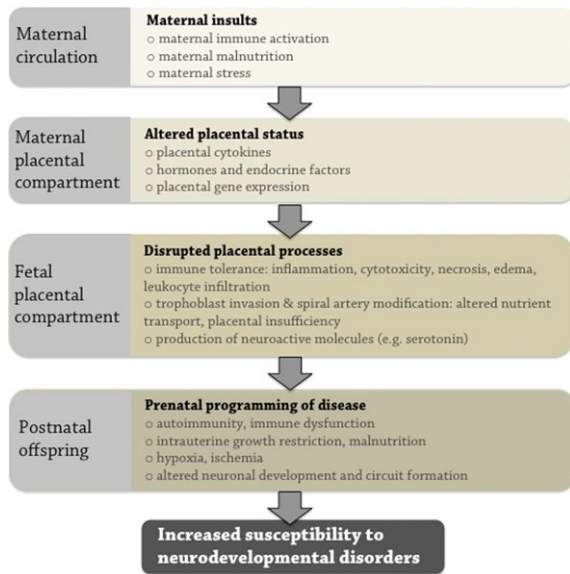


Figure 2 A placental role in developmental programming. Maternal and intrauterine challenges are necessarily conveyed to the developing offspring via the placenta. Maternal insults such as immune activation, malnutrition and stress result in altered composition of the maternal blood, which descends through the spiral arteries to fill the placental blood spaces. Changes in placental cytokines and endocrine factors can alter placental gene expression at the maternal–fetal interface. In light of the critical role of signaling factors in regulating normal placental processes, these alterations can further disrupt the maintenance of immune tolerance, progression of trophoblast invasion and spiral artery modification, or the *de novo* production of neuroactive molecules in the placenta. Placental pathophysiology contributes to a variety of obstetric complications and impairments to fetal development, such as hypoxia, growth restriction or immune dysregulation. These challenges further elaborate detrimental effects on early brain development, increasing susceptibility to neurodevelopmental disorders.

cause the disorders in subsets of individuals seems likely but remains to be firmly established. Studies of animal models of intrauterine infection and IUGR, where gestational challenges are confined to the uteroplacental compartment, demonstrate that primary insults to the placenta can manifest in perinatal brain damage in the offspring. Rodents, ewes and rabbits subjected to such placental challenges exhibit a variety of neuropathologies, including altered astrocyte development, microglial activation, white-matter damage and impaired blood brain barrier integrity (Hutton et al., 2008; Bassan et al., 2010). Notably, uteroplacental inflammation is sufficient to induce the expression of the apoptotic markers, caspase-3 and 4-hydroxynonenal, by Purkinje cells of the fetal ovine

cerebellum (Hutton et al., 2007). This is reminiscent of the Purkinje cell loss characteristic of autistic brains and observed in other neurodevelopmental disorders such as schizophrenia. It will be interesting to further assess the downstream effects of primary insults to the placenta on offspring behavioral development.

Furthermore, the placenta is known to regulate the synthesis of neuroactive factors throughout gestation that could influence fetal brain development (Petraglia et al., 2010). Recent findings in mice demonstrate that the placenta serves as a major source of serotonin to the fetal forebrain (Bonnin et al., 2011). Delivery of the precursor tryptophan through the maternal uterine artery leads to accumulation of newly synthesized serotonin in the placenta and fetal circulation, demonstrating the ability of the placenta to synthesize serotonin and transport it to the fetus. In contrast, delivery of a tryptophan hydroxylase antagonist to the placenta sufficiently inhibits placental serotonin synthesis and reduces levels of forebrain serotonin in corresponding embryos. These findings contribute to a growing number of studies that illuminate the key role of the placenta in *de novo* synthesis of neuroactive factors that are necessary for normal brain development (Hirst et al., 2009; Petraglia et al., 2010). Interestingly, placental infection and inflammation is associated with disruptions to the kynurenine/tryptophan pathway in the placenta, which may have corresponding effects on serotonin production and neural development.

The placenta is also a primary hematopoietic stem cell (HSC) niche during pregnancy, harboring a large population of HSCs during midgestation that are believed to seed the fetal liver (Gekas et al., 2005). Importantly, HSC development occurs in the placental vasculature independently of blood flow, supporting the finding that the placenta itself produces definitive hematopoietic cells that encompass both myeloerythroid and lymphoid potential (Rhodes et al., 2008). Thus, prenatal insults that influence placental physiology may also impact placental HSC development and postnatal immunity. Indeed, development of the immune system and responses of effector immune cells are influenced by early life environments and changes in microenvironmental cues such as cytokines (Sobrian et al., 1997; Coe and Lubach, 2000). In addition, altered immunity is frequently associated with neurodevelopmental disorders, such as schizophrenia and autism spectrum disorders (Patterson, 2009; Onore et al., 2011). It will be important to assess whether levels or properties of placental HSCs are altered by such prenatal insults as intrauterine infection.

Additional multidisciplinary studies are needed to elucidate the mechanisms by which the placenta guides normal fetal brain development and to gain insight into its role in the developmental programming of long-term health and disease. Specifically, additional models that involve primary insults to the placenta itself, rather than secondary effects on the placenta resulting from primary maternal challenge, will help focus research on placenta-specific effects on fetal development in the absence of confounding maternal factors. Lentivirus-mediated, placenta-specific transgenesis (Okada et al., 2007) and the utilization of transgenic mice harboring placenta-specific drivers such as trophoblast-specific protein alpha (*Tpoba*) and placental lactogens (*Pl1* and *Pl2*) will facilitate studies on the effects of targeted placental manipulations on offspring development. It will be particularly important to determine the effects on disease-relevant behaviors and neuropathology. Finally, the study of placental responses to maternal or intrauterine insults offers the potential to identify early targets for prevention of later-life disease. Such promise can be seen with the increasing use of prenatal magnesium sulfate for promoting fetal neuroprotection and preventing cerebral palsy and substantial motor dysfunction in at-risk infants (Doyle, 2012). While the precise basis for this protection is unclear, several studies demonstrate anti-inflammatory, antiapoptotic and vasodilatory properties of magnesium sulfate in the placenta (Kovac et al., 2003; Holcberg et al., 2004; Dowling et al., 2012). Further studies into the role of the placenta in regulating fetal development will shed light on how alterations in a variety of interactions at maternal–fetal interface may form the basis of early life programming of neurological, metabolic, as well as immunological disorders.

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