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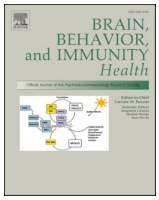

The role of the placenta-brain axis in psychoneuroimmune programming

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ABSTRACT

Gestational exposures have enduring impacts on brain and neuroimmune development and function. Perturbations of pregnancy leading to placental structure/function deficits, cell stress, immune activation, and endocrine changes (metabolic, growth factors, etc.) all increase neuropsychiatric risk in offspring. The existing literature links obstetric diseases with placental involvement to offspring neuroimmune outcomes and neurodevelopmental risk. Psychoneuroimmune outcomes in offspring brain include changes to microglia, cytokine/chemokine production, cell stress, and long-term immunoreactivity. These outcomes are altered by structural, anti-angiogenic/hypoxic, inflammatory, and metabolic diseases of the placenta. This fetal programming occurs via direct placental passage or production of factors which can act directly on fetal brain substrates, or indirectly via action of circulating factors on intermediates in the placenta. Placental neuroendocrine, vascular/angiogenic, immune, and extracellular vesicular mechanisms are detailed. These mechanisms interact within various placental and pregnancy conditions. An increased understanding of the placental origins of psychoneuroimmunology will yield dividends for human health. Identifying maternal and placental biomarkers for fetal neuroimmune health may also revolutionize early diagnosis and precision psychiatry, empowering patients to make the best healthcare decisions for their families. Targeting placental mechanisms may be a valuable approach for the prevention and mitigation of intergenerational, lifelong neuropathology.

1. Introduction

Health in pregnancy and offspring neuroprogramming are linked via placental mechanisms. For instance, the pro-inflammatory, hypertensive placental disease of pregnancy, preeclampsia, is associated with increased offspring neuroinflammation in preclinical models and with neuroinflammatory disorders such as cerebral palsy, epilepsy, and stroke (Gumusoglu et al., 2020a; Barron et al., 2021; Kong et al., 2022; Prins et al., 2018). Prenatal maternal stress is similarly associated with increased neuroinflammation in offspring, including increased microglial reactivity in fetal and adult brain, central nervous system cytokines, and changes to brain lymphocytes (Kim et al., 2021; Beversdorf et al., 2018; Bittle et al., 2018; Bronson et al., 2014; Diz-Chaves et al., 2012, 2013; Gilman et al., 2016; Goldstein et al., 2016; Klein et al., 1995; Merlot et al., 2008; Udagawa et al., 2016). To move the field of psychoneuroimmunology (PNI) forward, consideration of the mechanisms of placental-fetal brain programming and impacts on offspring brain health across the lifespan, beginning from its earliest stages, is required (Fig. 1). From gestational diseases to stress, our work and others' reveals that prenatal exposures program offspring neuroinflammatory phenotypes via multiple placental mechanisms (Fig. 2) (Gumusoglu et al., 2017a, 2018, 2020b, 2021a, 2022a). This work may provide new windows into health innovation in PNI, including into the detection, treatment, and prevention of intergenerational neuropsychiatric disease.

2. Studies of placental disease and neuropsychiatric risk

The placenta is a key regulator of fetoplacental physiology and adaptation in pregnancy. Placental processes shape the fetal environment and program developing fetal tissues (Myatt, 2006). Diseases and syndromes of pregnancy involving placental pathology are known risk factors for neurologic and psychiatric disorders in offspring. Placental pathologies can broadly be understood as involving disruptions to multiple domains: 1) structure, morphogenesis, and/or invasion (e.g., placenta accreta, placental insufficiency, lesions, or trauma), 2) angiogenesis, perfusion, and hypoxia (e.g., preeclampsia, infarction, vasculopathy), 3) inflammation (e.g., viral or bacterial infection), and 4) metabolism (e.g., gestational diabetes) (Fig. 2). For the purposes of

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Fig. 1. Serena Banu Gumusoglu: My research goal is to understand the molecular placenta-brain mechanisms by which disorders of pregnancy increase risk for neurodevelopmental disorders, with a particular focus on neuroimmune mechanisms. My PhD work, under the mentorship of psychiatrist-scientist Dr. Hanna Stevens at the University of Iowa, revealed the role of chronic maternal stress and elevations in IL-6 and IL-17a on offspring neurodevelopmental and psychoneuroimmune outcomes with relevance to autism and other neurodevelopmental disorders. My postdoctoral work complemented my neurodevelopment-focused doctoral work with training in reproductive biology under the mentorship of Dr. Mark Santillan, a high-risk obstetrician-scientist at the University of Iowa Hospitals and Clinics. In the Santillan Lab, I turned my focus to the anti-angiogenic, pro-inflammatory placental disorder of pregnancy preeclampsia, which is among the fastest growing and most prevalent obstetric diseases globally. Mechanisms of preeclampsia are heterogeneous and it has no known cure. Preeclampsia is associated with increased offspring risk for learning differences, autism, mood disorders, and more. Underlying programming mechanisms are unclear. Our work revealed a novel role for altered G protein coupled signaling, and in particular serotonin, in neurovascular and neurodevelopmental dysfunction in offspring of preeclamptic pregnancies. My own laboratory, founded in January of 2024, extends this work to examine mechanisms of psychoneuroimmune programming by placental factors in preeclampsia and other obstetric conditions. This work is supported by the Burroughs Wellcome Fund and the Brain and Behavior Research Foundation. Photograph by Justin Torner.

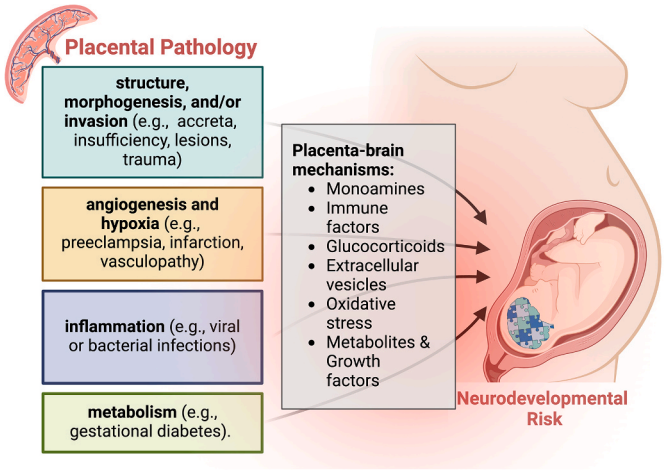

Fig. 2. Multiple molecular mechanisms may transmit signals from pathological placenta to the developing fetal brain. Diseases of pregnancy involve multiple forms of placental pathology. These including disrupted placental structure, morphogenesis, or invasion of placental cells, as in placental trauma, placental insufficiency, and placenta accreta, respectively. Disorders of placental angiogenesis and hypoxia such as preeclampsia are among the most common disorders of pregnancy. Inflammatory complications of pregnancy may result from bacterial or viral infection or even psychiatric stress. Finally, disorders such as gestational diabetes lead to metabolic pathology in the pregnant person and placental tissues. These clinical conditions have overlapping and complex etiologies, often invoking multiple placental mechanisms. Multiple molecular mechanisms may also be responsible for transmitting factors involved in placental pathology to the developing fetal brain and immune system. These mechanisms include monoamines and neurotransmitters, immune factors, glucocorticoids, extracellular vesicles, oxidative stress, and metabolic and growth factors. To advance the field of psychoneuroimmunology, future studies must determine the role of these various mechanisms in programming neuroimmune health of the exposed fetus. This will yield targets for the treatment, detection, and prevention of prevalent neurodevelopmental and neuropsychiatric disorders in their earliest stages. Made with BioRender.

organizing this brief review, structural and vascular mechanisms have been grouped and inflammatory and metabolic mechanisms have been grouped. Broadly, the first grouping relates to deficits in form, morphogenesis, and function of the placenta itself, while the second relates to mechanisms which invoke endocrine or signaling factors released into circulation. These domains are not independent but rather interact in diseases states, as exemplified by preeclampsia, which involves deficient placental vascularization, hypoxia, deficient angiogenic and growth factor production, pro-inflammation, and altered metabolism (Gormley et al., 2017; Mao et al., 2013; Tal, 2012).

2.1. *PNI programming and placental structural and vascular defects*

Clinical study of placental structural deficits, lesions, or trauma has revealed many, broad impacts on offspring neurodevelopmental and PNI outcomes (Linduska et al., 2015). Preclinical work similarly reveals that placental insufficiency, defined as inadequate growth or implantation of the placenta, causes increased offspring anxiety and cerebrovascular dysfunction (Girardi et al., 2015). While moderate placental injury after pregnancy trauma does not alter human motor development at 1 year of age (van der Knoop et al., 2019), severe placental trauma often causes hypoxic-ischemic injury, which is robustly linked with neurodisability and cognitive and motor delays in human cohorts (Bartha et al., 2004; Redline, 2008). In more severe cases, as in placental abruption leading to fetal hypoxic-ischemic encephalopathy (HIE), human infants exhibit lymphoid cell accumulation, delayed neurodevelopment, and increased serum Tau, a marker associated with neuronal injury and neuroinflammation (Fialova et al., 2017). In perinatal hypoxic injury, levels of circulating IL-1, IL-6, and TNFα are associated with neurologic symptoms at 1 year of age (Foster-Barber et al., 2001).

As with structural deficits due to trauma, lesions, or other factors, vascular disruptions also lead to altered placental morphogenesis and form. Placental pathologies involving deficient angiogenesis and/or perfusion are associated with offspring neurodevelopmental deficits. Preeclampsia, which is marked by placental hypoxia and impaired placental angiogenesis (decreased vascularization, impaired spiral artery remodeling, decreased perfusion), is linked with 3-fold or more increased risk for autism spectrum disorder, neonatal stroke, and learning disability (Gumusoglu et al., 2020a). Fetoplacental malperfusion is caused by maternal inflammation and is sufficient to cause placental hypoxia, reduced placental thickness, and reduced flow through umbilical and uterine arteries. Exposure to placental malperfusion in a mouse model causes fetal cardiovascular and neuroinflammatory outcomes including increased microglia density (Eloundou et al., 2019).

Advanced maternal age (AMA) is another pregnancy complication associated with placental structural deficits. For example, AMA is associated with precocious trophoblast differentiation (increased early terminal differentiation of placental stem cells into giant cells and syncytiotrophoblasts). Exposure to AMA placenta alters transcriptional heterogeneity in the murine brain (Kokorudz et al., 2022). For example, in a mouse model of AMA, offspring fetal brain has differential expression of PNI-relevant transcripts including *HIVEP2*, which regulates neuroinflammation (Takao et al., 2013), and KANSL1, which has been

investigated as a "master … immune-response gene" (Fejzo et al., 2021).

Given that placental and fetal tissues have 80–90% overlapping genetic expression, genetic vulnerabilities may be shared between embryonic brain and placenta—embryonic brain abnormalities may derive from the same mutations, transcriptional changes, or epigenetic changes that drive obstetric disease (Del Gobbo et al., 2020). For example, environmental perturbations such as exposure to polychlorinated biphenyls, a neurotoxin, lead to overlapping changes in gene expression in mouse placenta and brain (Laufer et al., 2022). This observation may be capitalized on to advance our understanding of the specific effectors and underlying mechanisms of prenatal PNI programming and neurodevelopmental risk by obstetric disease.

2.2. PNI programming and placental inflammatory and metabolic conditions

Infectious and idiopathic placental inflammation have well-characterized impacts on offspring neurodevelopment and neuropsychiatric risk, as detailed elsewhere (Hsiao et al., 2012; Wu et al., 2000). Inflammatory placental conditions such as chorioamnionitis and chorionic plate meconium are associated with clinical HIE (Lv et al., 2020), which is linked to persistent neuroinflammation and neurodevelopmental delays in infants and children (Ziemka-Nalecz et al., 2017). Up to one third of mothers of infants with perinatal HIE may be diagnosed with chorioamnionitis, which has diverse and varying impacts on maternal, fetal, and placental immunology (Eloundou et al., 2019; Weitkamp et al., 2016). Intrauterine transmission of canonical "TORCH" organisms (*Toxoplasma gondii, Treponema pallidum*, Hepatitis B virus, Rubella virus, cytomegalovirus, and herpes virus simplex), as well as HIV and Zika, are major drivers of fetal brain injury secondary to placentitis in large animal models (Gutierrez-Exposito et al., 2020). Recent clinical and preclinical work on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy has revealed that infection of placental tissues drives placental proinflammation, which increases offspring neurodevelopmental risk (Shook et al., 2022).

Inflammatory placental conditions may drive fetal and neonatal brain damage and neuroinflammation relevant to clinical conditions in humans (Spinillo et al., 2014). Multiple convergent offspring brain endophenotypes have been described in clinical and preclinical work on placental inflammation: increased phagocytic or activated microglia; increased pro-inflammatory cytokine production by pericytes, astrocytes, and neurons themselves; loss of oligodendrocytes and/or increased astroglia (John, 2022); and disruption of immune modulatory signaling pathways (e.g., proteasome pathway, interferon response) (Gutierrez-Exposito et al., 2020; Ohyu et al., 1999; Ganguli et al., 2021). Patterns of injury may differ by etiology. Parasitic *Toxoplasma gondii* infection leads to fetal brain inflammation, microglial activation, and oligodendrocyte but not neuronal loss in a large animal model (Gutierrez-Exposito et al., 2020). Contrary to this, bacterial toxins (e.g., lipopolysaccharide, Group B *Streptococcus*) cause increased glial and neuronal apoptosis and microglial activation in humans and murine models (Lehnardt et al., 2006; Hava et al., 2006; Golan et al., 2005; Leviton et al., 2007). Benign inflammatory conditions of pregnancy such as prenatal maternal stress also cause placental inflammation, offspring neuroinflammation, and persistent deficits in brain function across preclinical and clinical studies (Bronson et al., 2014; Diz-Chaves et al., 2012, 2013; Gumusoglu et al., 2017a; Buynitsky et al., 2009; Coussons-Read et al., 2007; Hantsoo et al., 2019).

Placental inflammatory conditions often result in a fetal neutrophil and leukocyte response characterized as fetal inflammatory response syndrome (FIRS). FIRS is caused by innate immune activation by insults such as preterm premature rupture of the membranes, intra-amniotic inflammation, alloimmunity (e.g., Rh factor disease), intraamniotic infection, and autoimmune conditions. FIRS exposure is associated with a wide range of neurologic complications in human offspring spanning motor, verbal/language, cognitive, and social-adaptive domains (Mittendorf et al., 2003; Scher, 2020). In early pregnancy, FIRS may result in brain lesions and malformations that drive severe epilepsies and other deficits, as well as spontaneous loss. FIRS may cause chorioamnionitis which, in late gestation (e.g., second and third trimester), may lead to focal or multifocal fetal cerebral injury, gliosis, hemorrhage, or HIE associated with neurodevelopmental disorders and focal epilepsies (Ziemka-Nalecz et al., 2017; Mittendorf et al., 2003; Scher, 2020).

As with inflammatory placental disease, placental metabolic disruption also leads to changes in feto-placental-maternal signaling and endocrine milieus. Placental metabolic dysregulation, as in gestational diabetes, has well-evidenced ties to neurodevelopmental and life-long neuropsychiatric dysfunction in human cohorts (Ahmed et al., 2023; Van Dam et al., 2018; Shao et al., 2021). Gestational diabetes causes placental immaturity, necrosis, and hyper-angiogenesis (Jarmuzek et al., 2015), and is linked with offspring developmental delay (Sun et al., 2022) and cognitive dysfunction (Ahmed et al., 2023; Van Dam et al., 2018), among other neurodevelopmental outcomes (Shao et al., 2021) revealed by clinical studies. The gestational diabetes medication metformin is also linked to placental metabolic and differentiation phenotypes (Nashif et al., 2023) as well as child neurodevelopmental abnormalities (Deussen et al., 2023; Yuen et al., 2021). These impacts may be due in part to methylation changes; maternal plasma glucose is associated with serotonin transporter gene (*SLC6A4*) methylation in placenta, which may be risk factor for later serotonin dysregulation and neurodevelopmental diagnoses, as discussed below (section 3.1) (Song et al., 2022).

Environmental exposures during pregnancy also impact placental metabolism and fetal PNI and neurodevelopment. For example, rodent work reveals that maternal pesticide exposure influences transcriptomics similarly in placenta and fetal brain, disrupting oxidative stress and MapK signaling pathways implicated in neuroimmune health (Lesseur et al., 2023). Maternal phthalate exposure is similarly associated with placental metabolic changes and adverse offspring neurodevelopmental outcomes in a large, intergenerational cohort (Parenti et al., 2022). Environmental exposures in pregnancy may also drive DNA methylation changes in human placenta, altering expression of autism spectrum disorder (ASD)-relevant loci involved in synaptogenesis and neurogenesis, for example (Ravaei et al., 2023).

3. Mechanisms of placental PNI programming

Increase in neuropsychiatric risk due to pathologic exposures of pregnancy may be driven by placental pathology, as outlined above. These exposures converge on a set of molecular mechanisms which must be elucidated for the field to achieve targeted interventions, diagnostics, and cures. Multiple, interacting molecular placenta-brain mechanisms of PNI programming including monoamine, immune, glucocorticoid and extracellular vesicles are discussed here (Fig. 2).

3.1. Neuroendocrine factors

A variety of placentally-mediated endocrine factors impact fetal brain development and immune status (John, 2022). Placental monoamine metabolism, signaling, and production are implicated in neuropsychiatric disorders from ASD to anxiety (Hendricks et al., 2003; Sato, 2013; Yang et al., 2014). Preclinical and clinical studies reveal that the placenta is likely the sole source of serotonin to the fetus during early embryogenesis, sculpting neurodevelopmental processes including cell migration, synaptogenesis, and neurogenesis (Bonnin et al., 2011a, 2011b, 2012). As mentioned above, metabolic stress effects expression of serotonin transporter (*SLC6A4*) via epigenetic mechanisms in human placenta (Song et al., 2022). This mechanism may alter placental handling of serotonin with potential fetal PNI and neurodevelopmental impacts.

An emerging literature on the enzyme indoleamine 2,3-dioxygenase

(IDO), spearheaded by our group and others, links maternal and placental serotonin metabolism to psycho-obstetric risk via a serotonin-immune mechanism. Our recent work reveals that IDO activity in maternal circulation is decreased in preeclampsia and in peripartum depression (Gumusoglu et al., 2023a), complications of pregnancy which increase offspring neurodevelopmental risk. IDO serves as a regulatory switch, catalyzing L-tryptophan to N-formylkynurenine in the kynurenine pathway. This is the rate-limiting step in tryptophan catabolism via the kynurenine pathway, depleting tryptophan stores available for serotonin synthesis. Decreased IDO activity in pregnancy thereby increases serotonin synthesis in maternal and fetal circulation, as we and others have described (Gumusoglu et al., 2021b, 2022b, 2023a). IDO activity is regulated by cytokines such as IL-1 and IL-2, which are altered in preeclampsia (Raghupathy, 2013; Das, 2015; Walker, 2011; Fialova et al., 2004). Immune-regulated IDO activity may serve as a mechanistic switch, reducing kynurenine synthesis from tryptophan in favor of serotonin synthesis in preeclampsia and other inflammatory disease states (Myint et al., 2003). Decreased IDO thereby links inflammatory and serotonin signaling, serving as a mechanism by which prenatal immune factors might disrupt serotonin metabolism and serotonin circuit formation in the brain (Gumusoglu et al., 2021b, 2022b; Vignato et al., 2022). In fact, our group has shown that loss of IDO in a mouse model is sufficient to cause placental phenotypes consistent with preeclampsia (Santillan et al., 2015) and that offspring brain IDO levels are correlated with cerebrovascular health in a model of prenatal serotonin disruption and neurodevelopmental risk (Gumusoglu et al., 2023b). Given this, I hypothesize that reduced IDO in feto-placental tissues may inappropriately increase tryptophan metabolism to serotonin by the placenta, dysregulating serotonin circuit formation and cerebrovascular health in the developing fetal brain. Similar effects have been reported in maternal immune activation models and preeclampsia (Bonnin et al., 2011a, 2012; Gumusoglu et al., 2023b). Future studies by our group and others will test this hypothesis, as well as strategies for buffering IDO depletion to protect fetal brain development.

Dopamine systems in offspring brain are also impacted by conditions of pregnancy and by inflammatory insult. An extensive preclinical literature links bacterial and viral infection in pregnancy to altered offspring dopamine systems suggestive of clinical risk for schizophrenia and psychosis (Aguilar-Valles et al., 2020; Treadway et al., 2019). Stress in murine pregnancy results in placental inflammation, offspring dopamine neuron dysfunction, and dopamine-associated behavioral abnormalities (Bronson et al., 2014). In the developed brain, pro-inflammation decreases dopamine synthesis and signaling. For example, cytokines directly activate brain-resident immune cells to release factors such as reactive oxygen species, which contribute to protein aggregation and dopaminergic cell death in Parkinson's disease (Puspita et al., 2017). Intracellular pathways involved in cell growth and cytokine production are likewise regulated by reactive oxygen species (Puspita et al., 2017). In preclinical work, enrichment for microglia in dopaminergic brain regions relative to elsewhere in the brain after postnatal LPS administration supports the conclusion that dopaminergic systems may be particularly sensitive to PNI programming effects (Kim et al., 2000). While these studies provide compelling evidence that immune activation impacts postnatal dopaminergic circuits, similar studies examining prenatal dopaminergic development and function are required.

As with serotonin and dopamine, placental adrenaline and noradrenaline/norepinephrine monoamine neurotransmitter mechanisms are disrupted in placental disease and may impact PNI programming (Manyonda et al., 1998), though this is largely unexplored. Adrenaline regulates uterine atony/hypotony, inhibiting labor and delivery, and appears to be largely regulated by metabolic rather than inflammatory mechanisms (Mordak et al., 2016). Additional candidate neuroendocrine factors secreted by placental tissues which should be explored for a potential role in PNI programming include opioids and steroids. For example, urocortin peptides play a critical role in parturition and are expressed by the human placenta and fetal membranes (Reis et al., 1999). These peptides, which are implicated in pregnancy and placental health and regulate immune function (Petraglia et al., 2010), may be high-yield targets for mechanistic exploration of placenta-brain programming of PNI.

Glucocorticoids, canonical endocrine products of the physiologic stress, are an additional molecular mechanism for PNI programming. Glucocorticoids regulate neurogenic, synaptogenesis, and plasticity processes and modulate neurotransmission in mature and developing brain. Increased fetal glucocorticoid stress hormones are further associated with fetal brain macro- and microstructural abnormalities which may predispose offspring to neurodevelopmental disorders (Sandman, 2015; Kassotaki et al., 2021). Human placental 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) rapidly and efficiently converts active maternal cortisol to inactive cortisone, which is unable to bind mineralocorticoid receptors to propagate corticosteroid action. The placenta thereby buffers the fetus from maternal glucocorticoids (Benediktsson et al., 1997). Human exposure to xenobiotics that target and inhibit 11β-HSD2 (e.g., industrial chemicals such as dyes, antibiotics, etc.) induce mitochondrial oxidative stress and pro-inflammatory IL-6 production by microglia cells, as does mineralocorticoid receptor binding (Nashev et al., 2012). These drugs may theoretically increase placental glucocorticoid passage to the fetus and increase microglial reactivity, though this remains to be directly tested.

3.2. Immune mechanisms

Maternal immune activation is a significant risk factor for neurodevelopmental disorders in children (Han et al., 2021; Gesundheit et al., 2013; Hagberg et al., 2012; Kim et al., 2015), an observation which has motivated many causal, preclinical studies of feto-placental immune processes in brain programming. Many such studies have utilized the viral mimetic Poly I:C or material infection by the Gram-negative bacterial cell wall component, lipopolysaccharide (LPS). Our group previously detailed these gestational manipulations and their impacts on feto-placental inflammation and PNI outcomes include changes to brain cytokines, microglia and astrocyte immune factor expression, stress reactivity and circuits, inflammatory endocrine responses, and monoamine systems development (Gumusoglu et al., 2018). This field is complex and there are myriad immune mechanisms by which placenta-PNI programming in fetal life might occur. Here, I detail just a few discrete mechanisms which have been strongly implicated in PNI programming.

Our work and others' point to a role for placental IL-17 and upstream IL-6 mechanisms in PNI programming. Placental diseases ranging from preeclampsia (Lu et al., 2020; Eghbal-Fard et al., 2019; Molvarec et al., 2015; Pinheiro et al., 2013; Sowmya et al., 2015; Cornelius et al., 2016; Lockwood et al., 2008; Radulescu et al., 2016) to infection-associated spontaneous preterm birth (Bhati et al., 2023), placental insufficiency (Darmochwal-Kolarz et al., 2017), chorioamnionitis (Lawrence et al., 2018), and chronic stress (Bronson et al., 2014; Diz-Chaves et al., 2012; Gumusoglu et al., 2017; Mouihate et al., 2016; Veru et al., 2015) feature increased maternal-placental IL-17 and -6 and have a pathoetiology that is dependent on these cytokines (Eghbal-Fard et al., 2019). IL-17 promotes pathologic placental trophoblast migration, viability, and invasion via PPAR-γ/RXR-α/Wnt signaling (Zhang et al., 2022a). We previously found that maternal IL-17 is sufficient to cause offspring ASD-like phenotypes including glial, synaptic, and behavioral deficits in a mouse model (Gumusoglu et al., 2020b). This complements other preclinical reports that feto-placental T helper 17 (TH17) cells are a critical component of maternal immune activation impacts on offspring brain outcomes (Choi et al., 2016; Estes et al., 2016). Our group also reported that maternal IL-6 in murine pregnancy is sufficient to cause persistent changes to offspring cortical microglia in embryonic cortical plate and adult cortex (Gumusoglu et al., 2017). As with IL-17, placental

IL-6 has a central role in offspring PNI impacts of maternal immune activation and prenatal stress (Wu et al., 2017; Smith et al., 2007).

Complement systems in the placenta are another candidate immune mechanism for PNI programming in the context of placental and obstetric disease. For instance, recent preclinical work finds that prenatal stress reduces CCL2 and *Ccr2* expression and leukocyte counts in the placenta while increasing monocyte and microglia numbers in fetal mouse brain. Amniotic CCL2 is sufficient to drive offspring behavioral deficits in a mouse model and prenatal stress may drive feto-placental inflammation and offspring PNI outcomes via CCL2 mechanisms (Chen et al., 2023). Placental levels of the chemokine ligand 1 (CXCL1) and its cognate receptor (CXCR2), which are upregulated in chorioamnionitis, drive CXCL1/CXCR2 signaling, immune cell activation, and microgliosis in the fetal mouse brain (Chen et al., 2023). This work reveals that chorioamnionitis impacts on offspring neurologic disfunction may be mediated by placental-fetal brain CXCL1/CXCR2 mechanisms.

Placental macrophages are an additional mechanism by which pro-inflammatory signals may be transmitted to offspring brain. In fact, mammalian placental macrophages and brain resident microglia have common origins in the fetal yolk sac and may therefore share molecular signatures (Ginhoux et al., 2010). Work in a pro-inflammatory gestational obesity mouse model revealed increased offspring brain CD11b + cell reactivity relative to unexposed controls. In this model, fetal offspring brain CD11b + cell reactivity was correlated with placental pro-inflammatory cytokine production in response to a later LPS immune challenge (Edlow et al., 2019). These findings suggest that brain and placental immune systems are primed in concert by chronic maternal immune activation models such as obesity. Placental macrophages may be an accessible and reliable biomarker of fetal brain immune status, though this requires additional study.

3.3. Extracellular vesicles

Extracellular vesicles (EVs) are an additional molecular mechanism for endocrine signaling between placental and maternal tissues and the fetus. EVs are nanoscale (30–150 nm) lipid bilayer membrane-bound vesicles secreted by cells into the extracellular space (Kalluri et al., 2020). Studies in mice further reveal that EVs travel bi-directionally across the placenta and from placenta to targets in both fetal and maternal tissues (Kang et al., 2023). In neonatal mice, developmentally comparable to fetal humans, EVs consumed via lactation cross intestinal and blood-brain barriers to penetrate the offspring brain. Within the fetal brain, these EVs accumulate in the hippocampus, cortex, and cerebellum, where they alter dendritic structure and brain function (Zhou et al., 2022).

Cells package EVs with nucleic acids, proteins, and lipids that evade degradation due to protection by the EV bilayer membrane (Szatanek et al., 2017; Yates et al., 2022; Ouyang et al., 2014). The endocrine function of EVs in cancer and reproduction has been described, with placenta and tumors being some of the most prevalent physiologic sources of EVs (Kazemi et al., 2021). EVs regulate and promote the cell processes necessary for rapid tissue development including cell invasion, vascular remodeling and angiogenesis, and immunomodulation (Kazemi et al., 2021). Circulating EVs have been proposed as a 'liquid biopsy' for biomarker identification in diseases of pregnancy such as gestational diabetes and preeclampsia (Tannetta et al., 2017), and for neurodevelopmental disorders (Gillet et al., 2016; Jin et al., 2018). EVs traffic antigens and immune molecules, regulating immune suppression and activation throughout human pregnancy (Morelli et al., 2022).

EVs shuttle brain-relevant factors, including miRNAs, serotonin, and microproteins, from placenta to the developing embryonic brain. Murine trophoblast-derived EVs contain miRNAs and small nucleolar RNAs which are enriched for fetal brain targets and alter the transcriptomic profile of cultured neural progenitors. Proteins and mRNA contained within these EVs are also associated with immune system and cell stress response ontological pathways and target thymus and brain-enriched mRNAs (Kinkade et al., 2023), suggesting neuroimmune effects. This preclinical work complements clinical evidence that EVs transport immunomodulatory cargos in chorioamnionitis and are implicated in perinatal brain injury and neuroinflammation (Gall et al., 2022; Redline, 2022). Placental-derived EVs are sufficient to increase brain CXCL1 expression in neonatal brain, which is prevented along with neurologic injury and microglia activation when EV generation is inhibited. Data from clinical populations similarly reveals a neuroimmune regulatory role for EVs. Serum EVs from children with ASD stimulate pro-inflammation in microglia, for example (Tsilioni et al., 2018). Due to the difficulty accessing fetal EVs, studies directly examining their quantities and/or cargos in the context of pregnancy complications are limited. Ongoing work by our group and others examines fetal EV changes with diseases of pregnancy such as preeclampsia, as well as the mechanisms by which EVs are selectively packaged in placental cells, deployed to act on targets in the fetal brain.

3.4. Additional mechanisms

In addition to the mechanisms discussed above, oxidative stress, metabolic, growth factor, and nutritional mechanisms have also been implicated in prenatal PNI programming. Often, these mechanisms interact with others discussed here in complex ways and at multiple levels of biology. For example, LPS in murine pregnancy, which causes reduced placental perfusion and vascular endothelial damage, pro-inflammation, and increased antioxidant expression, increases fetal microglial activation across cortical regions (Diz-Chaves et al., 2012; Hava et al., 2006; Golan et al., 2005; O'Loughlin et al., 2017; Cai et al., 2000; Rousset et al., 2006; Oskvig et al., 2012; Schaafsma et al., 2017; Urakubo et al., 2001; Lin et al., 2012; Lin et al., 2014). In a mouse model, these microglial impacts are mediated by maternal melatonin, an anti-coagulant and antioxidant (Lee et al., 2019).

Alterations to the maternal gut microbiome with stress in pregnancy are also sufficient to alter murine offspring brain outcomes including fear extinction behavior, microglia activation, and synaptic density (Zeng et al., 2024). This prenatal programming of PNI endophenotypes by prenatal stress is modified by probiotic supplementation in rats (Zeng et al., 2024). Satiety-related maternal leptin signaling stimulates pro-inflammatory cytokine release from placental cells (Lappas et al., 2005), and leptin alters developing dopaminergic systems in offspring after prenatal maternal immune activation in a rodent model (Aguilar-Valles et al., 2012). Preclinical work further reveals that maternal diet and obesity prime placental and fetal brain macrophages for increased reactivity (Edlow et al., 2019), and perinatal diet also alters PNI outcomes in enduring ways via maternal immune and epigenetic mechanisms (Bolton et al., 2014).

Disorders of placentation and placental function such as preeclampsia involve deficient angiogenic and growth factor expression (Steinberg et al., 2009). Placental growth factor (PLGF) is necessary for normal placental development and is decreased in preeclampsia, as is circulating vascular endothelial growth factor (VEGF). These pro-angiogenic growth factors are required for normal brain growth, development, and function, as demonstrated in studies of *Plgf*$^{-/-}$ mice (Kay et al., 2018). PLGF plays a vital role in neuroimmune interactions in the spleen which underlie broader physiology, and reduced action of the PLGF receptor VEGFR1 after tissue injury reduces microglial infiltration in a murine model (Huang et al., 2013). Tight regulation of these growth factors is vital for pregnancy health. For example, gestational stress and depression are associated with increased VEGF, placental necrosis, inflammation, and hemorrhage in cases of spontaneous pregnancy loss (Marinescu et al., 2014).

Together, the findings discussed here demonstrate that placental growth and angiogenic factor mechanisms, as well as vascular, structural, immune, and metabolic mechanisms, may drive fetal PNI outcomes after exposure to disorders of pregnancy such as preeclampsia. As

highlighted by the multifactorial and heterogeneous disorder preeclampsia, these mechanisms are often overlapping within pathology and do not 1:1 represent clinical disease or offspring brain impacts. For example, preeclampsia, a dysangiogenic, pro-immune disease of pregnancy, acts via multiple complex and interacting mechanisms (e.g., metabolic, vascular, hypoxic, etc.) to influence the developing fetal brain (Gumusoglu et al., 2020a; Leavey et al., 2015). These mechanisms each have impacts at the epigenetic, transcriptional, translational, endocrine and paracrine signaling, and cellular/tissue function levels, as discussed above. At the functional level, preeclampsia has sometimes devastating, and sometimes subtle or no effects on the developing offspring brain (Gumusoglu et al., 2020a). Thus, to understand the broad range of impacts each condition of pregnancy may have on the developing offspring brain, multiple simultaneous approaches are required: 1) the biology of pathologic exposures (e.g., diseases of pregnancy) must be characterized in detail, 2) placental pathology must be understood at multiple levels, and 3) mechanisms of placental impact on fetal brain must be discovered and tested. While each of these efforts may be pursued separately, they are highly interacting and understanding of each begets that of the other.

4. Limitations

Despite great strides over the last several decades to elucidate the placental mechanisms of neurodevelopmental disorders and PNI outcomes, this work has been limited by a number of pervasive issues. One major confound in these studies is prematurity, which itself is associated with exacerbations to the fetal neuroimmune milieu and multiple placental conditions discussed here, such as preeclampsia (Bhati et al., 2023; Krishnan et al., 2013). Placental conditions should be considered for their impact on brain development independently from that of prematurity and other factors which are colinear with it, such as low birth weight, lung immaturity, and exposure to increased medical/-environmental stress (e.g., heel stick). There are many other risk factors for abnormal offspring neurodevelopment which are also risk factors for obstetric disease: maternal obesity (and high fat diet), exposures to environmental toxicants, racism, trauma, and early childhood adversity, to name only a few (Brunton, 2013; Kim et al., 2017; Mychasiuk et al., 2011; Gralewicz et al., 2009; Girchenko et al., 2018; Oyana et al., 2015; Spradley et al., 2015). For example, prior work finds increased adverse childhood events (ACEs) in women with preeclampsia (Gillespie et al., 2019; Racine et al., 2022); ACEs increase risk for intergenerational neuropsychiatric disease, an association further confounded by genetic risk among high ACE exposure and psychiatric cases (Gillespie et al., 2019; Hughes et al., 2017; Zhang et al., 2022b). Animal models are an important approach to understanding intergenerational causality without layered environmental, clinical, and genetic factors which are difficult to parse in human cohorts.

Sex is another critical factor which should be examined. Male vulnerability has been noted in multiple PNI programming mechanisms and outcomes (Bronson et al., 2014; Konsman et al., 2020). Additionally, clinical studies of offspring resulting from pregnancies with placental disease often bias towards less severe disease. As much as 50% of pregnancies with histologic chorioamnionitis spontaneously terminate (Pugni et al., 2016); those that do not may reflect distinct pathoetiology. Resulting studies may be skewed by survivorship bias, a form of selection bias in which surviving cases exhibit increased resilience to insult, as discussed in other areas of biomedical research (Pasqualetti et al., 2023). Finally, as others have reasoned, caution must be observed when attributing phenotypes to neuroinflammatory processes (Estes et al., 2014). Multiple endpoints, ideally at several levels of analysis, should be demonstrated prior to concluding that placental immune mechanisms are responsible for intergenerational PNI effects.

5. Conclusions and future Directions

Despite challenges and limitations, novel solutions are plentiful and pave an exciting path forward. First, the field should consider that PNI trajectories begin before birth. Our work and others' finds that placental conditions program the developing brain and neuroimmune system in enduring ways and across levels of analysis (e.g., from epigenome to transcriptome to protein and cell function) (Gumusoglu et al., 2017). Preclinical studies have highlighted a role for feto-maternal-placental immune activation in programming age-related deficits, including microglial abnormalities, synaptic loss, neuronal death, spatial learning and memory deficits, increased amyloid precursor protein, and mislocalized and hyperphosphorylated tau (Krstic et al., 2012; Hao et al., 2010). As the field's understanding of neurodegenerative diseases shifts to incorporate neuroimmune pathophysiology (Glass et al., 2010), it becomes ever more important to question the role of PNI programming by placental processes in these diseases. It remains unclear whether prenatal microglia programming by placental factors increases neurodegeneration risk.

Next, the field should work to develop placental biomarkers, and peripheral maternal correlates, of fetal neuroimmune health. Such biomarkers may pay dividends in the early diagnosis, treatment, and prevention of neurodevelopmental disease. Identification of offspring risk biosignatures accessible via the maternal circulation, such as placental- or fetal brain-derived ECVs (Goetzl et al., 2019), may reimagine the future of fetal precision medicine. To empower patients to make the best decisions for themselves and their families, a comprehensive understanding of the risks and benefits of both medical outcomes and possible interventions is required. Preventative care, which is often associated with low risk and high potential reward, thus emerges as an important goal for the advancement of fetal precision medicine.

Future therapies should take advantage of known placental mechanisms and their role in PNI to prevent or ameliorate pathologic sequelae. Clinical trials are evaluating transplantation of mesenchymal stem cells to treat HIE; these cells attenuate pro-inflammation following and promote neurogenesis and cell repair (Park et al., 2021). Placental mechanisms may be high-yield targets for intervention. For example, the placenta epigenome is readily modified by increased social support in pregnancy (Tesfaye et al., 2023). More precise understanding of PNI in fetal life and on the role of the placental mechanisms discussed here may reveal novel and effective strategies for the detection, prevention, and treatment of psychiatric disorders in their earliest, prenatal stages.

CRediT authorship contribution statement

Serena B. Gumusoglu: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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