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Prenatal and postnatal contributions of the maternal microbiome on offspring programming

Eldin Jašarević, Tracy L. Bale*

Center for Epigenetic Research in Child Health and Brain Development, Department of Pharmacology, University of Maryland School of Medicine, Baltimore, MD 21230, United States

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ABSTRACT

The maternal microbiota is positioned to regulate the development of offspring immunity, metabolism, as well as brain function and behavior. The mechanisms by which maternal microbial signals drive these processes are beginning to be elucidated. In this review, we provide a brief overview on the importance of the microbiome in brain function and behavior, define the maternal vaginal and gut microbiota as distinct influences on offspring development, and outline current concepts in microbial origins of offspring health outcomes. We propose that the maternal microbiota influences prenatal and early postnatal offspring development and health outcomes through two overlapping processes. First, during pregnancy maternal gut microbiota provide metabolites and substrates essential for fetal growth through metabolic provisioning, driving expansion and maturation of central and peripheral immune cells, and formation of neural circuits. Second, vertical transmission of maternal microbiota during birth and in the early postnatal window elicits a potent immunostimulatory effect in offspring that induces metabolic and developmental transcriptional programs, primes the immune system for subsequent microbial exposure, and provides substrates for brain metabolism. Finally, we explore the possibility that environmental factors, such as malnutrition, stress and infection, may exert programmatic effects by disrupting the functional contributions of the maternal microbiome during prenatal and postnatal development to influence offspring outcomes across the lifespan.

1. Background

The recent enactment of a "zero tolerance" policy by the United States government on unlawful immigration that forced separation of parents from their young children in detention camps has reignited global attention on the detrimental effects of early-in-life adversity. These recent cases of parental separation and loss of a caregiver are only one part of a much larger global health concern (Boullier and Blair, 2018; Dozier and Bick, 2007; Masten et al., 1990). Maternal adversity, manifested in the form of malnutrition, chronic stress, or immune activation during the perinatal period is associated with negative health outcomes that offspring can endure across the lifespan (Bale, 2015). An unprecedented effort from clinical and preclinical researchers over the last century has led to the discovery of numerous mechanisms that mediate offspring risk, including shifts in the composition of the maternal milieu, changes in placental function, and epigenetic modifications of germ cells and somatic reproductive tissues (Bale, 2015; Morgan et al., 2019).

Technological advances over the last decade have revealed other facets of the maternal milieu in contributing to offspring outcomes, namely the trillions of microorganisms that reside on or within our bodies (Cryan and Dinan, 2012; Kuczynski et al., 2012; Mueller et al., 2015; Prince et al., 2014). These communities of microorganisms, including fungi, protozoa, Archaea, viruses, and bacteria outnumber the total mammalian cell numbers in the human body, and their genetic information is estimated to be greater than that of the human genome (Forster et al., 2019; Pasolli et al., 2019; Qin et al., 2010). This genetic repertoire of the microbiome provides extensive metabolic and immunological potential otherwise unavailable to the host (in this review, the term 'host' is used to specifically refer to the organisms that harbor the microbiota, e.g., the human host or rodent host) (Forster et al., 2019; Pasolli et al., 2019; Qin et al., 2010). Genetic and environmental factors influence microbiota composition and function, and these complex host-microbe interactions contribute to health and disease

* Corresponding author at: Departments of Pharmacology & Psychiatry, Center for Epigenetic Research in Child Health and Brain Development, HSF3, Room 9-171, University of Maryland School of Medicine, 670 W. Baltimore St., Baltimore, MD 21201, United States.
E-mail address: tbale@som.umaryland.edu (T.L. Bale).
URL: http://CERCH.UMaryland.edu (T.L. Bale).

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states (Bevins and Salzman, 2011; Byndloss et al., 2018; Cryan and Dinan, 2012; Gilbert et al., 2018; Kabouridis and Pachnis, 2015; Pronovost and Hsiao, 2019; Round and Mazmanian, 2009; Schmidt et al., 2018). Our relationships with these microbes begin before birth, become more direct during the birth process, and remain in reciprocal flux across the lifespan (Asnicar et al., 2017; Dominguez-Bello et al., 2010; Korpela et al., 2018; Pronovost and Hsiao, 2019; Yassour et al., 2018; Yatsunenko et al., 2012).

The increasing efforts to integrate microbiome science, psychiatry and neuroscience has provided critical insight into microbial contributions to brain development and behavior (Abdel-Haq et al., 2019; Bastiaanssen et al., 2018; Bravo et al., 2011; Cryan and Dinan, 2012; Foster et al., 2017; Fung et al., 2017; Diaz Heijtz et al., 2011; Jašarević et al., 2017, 2018; Kabouridis and Pachnis, 2015; Sampson and Mazmanian, 2015; Sarkar et al., 2018; Sherwin et al., 2018; Vuong et al., 2017; Warner, 2019). This work suggests that the mechanistic contribution of maternal microbiota and its metabolites during prenatal and early postnatal brain development may be distinct from other microbial mechanisms that act on brain health in adulthood or aging. During the prenatal period, metabolites, antibodies and substrates produced by the maternal gut microbiota may provide the necessary metabolic support for the molecular machinery involved in the formation of neural circuits (Koren et al., 2012; Nuriel-Ohayon et al., 2019; Gomez de Aguero et al., 2016; Thion et al., 2018). In studies comparing rodents devoid of any microorganisms, termed germ-free, and conventional mice, absence of a maternal microbiome is associated with deficits in immune development, blood-brain barrier formation, programming of the HPA stress axis, regulation of hypothalamic circuits involved in appetite regulation and energy balance, and maturation of microglia, the resident macrophages in the brain (Cryan & Dinan, 2012; Gomez de Aguero et al., 2016; Thion et al., 2018; Erny et al., 2015; Frost et al., 2014; Matcovitch-Natan et al., 2016; Nuriel-Ohayon et al., 2019; Sudo et al., 2004). While these studies demonstrate that a complete absence of maternal microbiota exert profound effects on developing offspring, very little is known about compositional differences of an intact maternal microbiome and lasting phenotypic outcomes in offspring. Indeed, recent work in conventionalized mice has shown maternal stress experienced during the first week of pregnancy exerts lasting effects on maternal gut microbiota composition and is associated with outcomes in adult offspring (Jašarević et al., 2017). This may indicate that other maternal exposures, such as malnutrition and infection, also converge onto the maternal gut microbiome to drive programmatic effects on the developing brain.

At birth, vertical transmission of maternal microbiota to offspring supports postnatal growth and development (Funkhouser and Bordenstein, 2013). A variety of factors, including birth mode, diet and antenatal exposure to antibiotics, impact maternal-to-offspring transmission that may influence offspring outcomes in humans (Dominguez-Bello et al., 2010; Cox and Blaser, 2015Bokulich et al., 2016; Ferretti et al., 2018). Rapidly following birth, assembly of gut bacterial communities occurs as a dynamic process that is influenced by age-associated events such as dietary transitions (Subramanian et al., 2014). The developmental periods during which specific bacteria contribute to this assembly process appears to be non-random and conserved during infancy and childhood (Subramanian et al., 2015). This process introduces microbial genomes that encode metabolic and enzymatic pathways previously unavailable to the host. This includes the ability to metabolize dietary components and transform these substrates into vital sources of energy required for development of many tissues, including the brain (Goyal et al., 2015). For instance, the microbial metabolite butyrate is used as a fuel source in mitochondria to sustain $NADH/NAD^+$ balance and energy homeostasis, supporting that microbiota-derived metabolites are associated with energy metabolism to distant tissues including the brain (Donohoe et al., 2011). Thus, these patterns of gut microbiota maturation provide a unique readout of healthy growth and development in infancy and childhood, and deviations from this program may be associated with negative health outcomes (Subramanian et al., 2014). Thus, an uncoupling between maternally acquired microbiota, microbial capacity to harvest energy and nutrients, and the metabolic demand of the developing brain during this early-in-life period may contribute to lasting programmatic effects on brain and behavior.

While presented here separately for simplicity, we envision these processes as mutually inclusive and reflecting overlapping modes by which maternal microbiota may influence offspring development. Thus, this integrated and interdisciplinary framework may yield novel insights about complex neuropsychiatric pathogenesis and provide a starting point for a new class of biomarkers and therapeutic interventions. In this review, we discuss (i) microbiome effects central to neural and behavioral outcomes; (ii) the role of the maternal microbiota in prenatal and postnatal development; and (iii) maternal microbiota contribution to sex-specific offspring stress reprogramming.

2. Microbiome influence on brain and behavioral phenotypes

The assertion that the microbiome is a critical factor in human health is not novel (Metchnikoff, 1921). Microbiology-oriented fields have long recognized that the effects of host and and microbiota on a phenotype are interdependent, but application of such principles in neuroscience is lagging (Stappenbeck and Virgin, 2016). A variety of factors, such as mouse strain background, sex, age and diet, may mediate neural and behavioral readouts via converging effects on the microbiome (Eberl, 2015; Ericsson et al., 2018; Franklin and Ericsson, 2017) (Fig. 1). This interplay between host and environmental factors, the microbiome and phenotype are highlighted in the proceeding sections.

2.1. Microbial status

From decades of research using germ-free model organisms, it is clear that presence of microbiota plays an essential role on nearly every aspect of host biology (Gordon, 1959; Hill and Artis, 2010; Hooper et al., 2012; Littman and Pamer, 2011). Transplantation of human microbiota into adult germ-free mice has proven to be a powerful approach in evaluating the mechanistic contribution of the human microbiome to clinically-relevant phenotypes and disease states (Blanton et al., 2016; Faith et al., 2014, 2010; Goodman et al., 2011; Lecuit et al., 2007; Ridaura et al., 2013; Samuel and Gordon, 2006; Turnbaugh et al., 2009b). For instance, transplantation of microbiota from twins discordant for obesity into adult germ-free mice recapitulated body mass and adiposity phenotypes in mice receiving microbiota from the obese twin but not the lean twin (Ridaura et al., 2013). Germ-free mice that overexpress alpha-synuclein show exaggerated motor deficits following colonization with the microbiota from patients with Parkinson's disease (Sampson et al., 2016). Most recently, germ-free mice colonized with microbiota from healthy infants or infants with cow's milk allergy showed that germ-free mice colonized with microbiota from infants with cow's milk allergy were more susceptible to anaphylactic responses to allergens (Feehley et al., 2019). As the human samples used in these studies were collected following confirmation of a clinical diagnosis, such as obesity, allergy or neurodegenerative disease, these studies demonstrate that the microbiome plays a role in the *maintenance* of disorders. However, it is currently unclear whether microbiota is mechanistically involved in the *etiology, progression* and *onset* of disorders. A particular challenge in answering such causal questions involves synchronizing human samples with the stage of development of the model organism to reveal development-specific contributions of the microbiome on outcomes.

The insights gained from studies in adult germ-free mice have important implications for studies investigating the role of microbiota in early life programming. It is increasingly clear that the brief window during which offspring transition from a sterile compartment to a

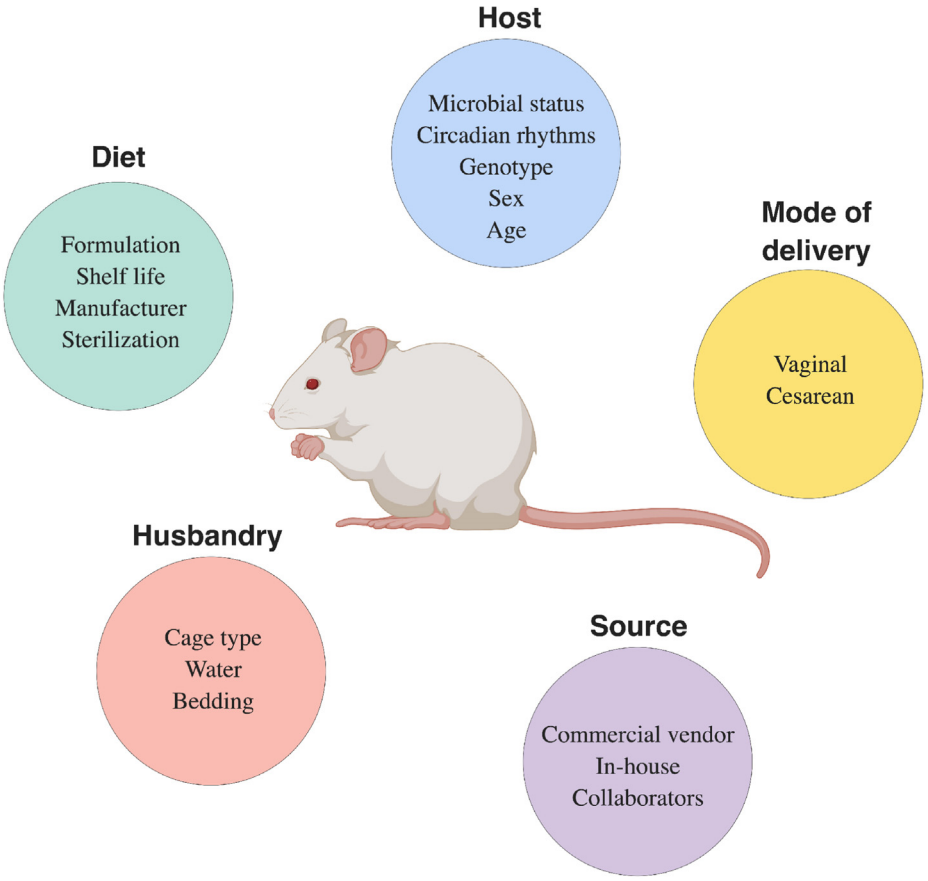

Fig. 1. Host and environmental factors that influence phenotype via the microbiome. The microbiota may be altered by host factors, diet, husbandry practices, and purchasing source of animals. Standardization of these factors for neuroscience research will ensure transparency and reproducibility of results.

microbe-rich environment represents an important window of opportunity for proper immune education that confer lasting effects on disease risk (Gensollen et al., 2016). Indeed, transcriptional programs involved in the acquisition of microbial tolerance are activated within two hours of birth in mouse intestinal epithelial cells, a process that is essential for innate immune recognition and lifelong intestinal host-microbe homeostasis (Lotz et al., 2006). Activation of intestinal epithelial cells is absent in mice delivered by Caesarean, further supporting the role of maternally acquired microbiota at birth in driving these processes. Given the high inter-subject variability of microbiota in human populations, novel methods are needed to assess the impact of colonization by unique communities on lasting offspring outcomes. One recently developed approach involves delivering mice by Caesarean and colonizing these mice with maternal microbiota (Jašarević et al., 2018). Another method involves surgical transfer of embryos to recipient females that harbor a desired microbial community, which allows for the uncoupling of host genetics and the microbiome (Ericsson and Franklin, 2015; Ericsson et al., 2015; Hart et al., 2018; Rosshart et al., 2019).

Extension of these methods that leverage clinical phenotypes and human microbial communities may yield novel translational model systems to investigate the lasting effects of microbial communities during this early life period on subsequent disease risk or resilience.

2.2. Genotype

The genetic background of inbred strains has been exploited for many decades in all areas of biomedical sciences. The most widely used inbred strains are C57BL/6, C57BL/10, C3H, CBA and BALB/c mice, which were initially developed for studies involving antitumor activity and immunogenicity for cancer biology and immunology. For instance, C57Bl/6 and BALB/c mice are prototypical type 1 helper T cell (Th1)- and Th2-type mouse strains, respectively, and produce fundamentally different innate and adaptive immune response profiles to allergen, bacterial and parasite challenges (Watanabe et al., 2004). For instance, following infection with the parasite *Leishmania major*, T cells from C57Bl/6 mice preferentially produce Th1 cytokines with high levels of interferon-γ (IFN-γ) and low levels of interleukin-4, whereas BALB/c mice favor Th2 cytokine production with low levels of IFN- γ and high levels of IL-4 (Watanabe et al., 2004). Macrophages from C57Bl/6 mice produce higher levels of tumor necrosis factor-α (TNF- α) and IL-12 than those from BALB/c mice following stimulation with lipopolysaccharide, the major component of the outer membrane of Gram negative bacteria that is recognized by toll-like receptor 4 (Watanabe et al., 2004). Conversely, BALB/c are resistant to experimental allergic encephalomyelitis (EAE) and induction of anaphylactic shock by ovalbumin (Levine and Sowinski, 1973). These strain differences in immunity are further compounded by well-established sex differences in immune responsivity (Klein and Flanagan, 2016). As such, it should come as no surprise that these inbred mouse strains, despite their genetic homogeneity, exhibit divergent patterns in microbial community composition and function that, in turn, mediate strain-specific immune homeostasis.

This 'host gene plus microbe' interdependence forces us to reconceptualize phenotypes as the interaction between specific microbiota and defined host genetic backgrounds. A recent study developed a non-germ-free approach to screen for specific commensal bacteria subsets that may induce inflammatory bowel disease (IBD) and identified commensal *Bacteroides* species (Bloom et al., 2011). Following antibiotic-mediated microbial depletion, commensal *Bacteroides* was inoculated into genetically susceptible and non-susceptible mice and induction of colitis and underlying immunopathology was observed in

susceptible hosts but not in non-susceptible hosts. Further, commensal Enterobacteriaceae bloomed in mice during the active phase of disease (Bloom et al., 2011). Transplantation of the colitis-enriched Enterobacteriaceae failed to induce disease in neither genetically susceptible nor non-susceptible mice, demonstrating that disease-associated microbiota alterations does not reflect underlying disease etiology (Bloom et al., 2011). From a practical viewpoint, the ability of commensal microbes to induce disease in certain genetic and environmental contexts, while innocuous in others, emphasizes the need to better understand baseline susceptibility among rodent strains and genetic backgrounds commonly used in neuroscience research.

The maternal immune activation (MIA) mouse model is a particularly relevant example of host gene-plus-microbe interactions that converge on neurodevelopmental and behavioral outcomes. In this model, pregnant dams are injected intraperitoneally with the synthetic double-stranded RNA (polyinosinic:polycytidylic acid, poly(I:C)), which mimics a viral infection (Smith et al., 2007). Exposed offspring exhibit various altered phenotypes, including altered immune response, metabolism, and behavior (Reviewed in Fung et al., 2017; Kentner et al., 2019; Pronovost and Hsiao, 2019). Surprisingly, MIA-associated behavioral phenotypes are dependent on the maternal gut commensal segmented filamentous bacteria (SFB), which drive differentiation and expansion of a unique T-cell subset known as T-helper 17 (T_H17) cells that produce the inflammatory cytokine interleukin 17a (IL-17a) (Choi et al., 2016; Kim et al., 2017). To investigate the importance of SFB in driving MIA-associated offspring phenotypes, a series of experiments compared C57BL/6 mice from Taconic Biosciences that are readily colonized by SFB and C57BL/6 mice from Jackson Laboratories (Jax) that lack SFB (Choi et al., 2016; Kim et al., 2017). In contrast to offspring from poly(I:C)-injected Tac dams, offspring from poly(I:C)-treated Jax dams failed to show any of the MIA-associated behavioral phenotypes (Choi et al., 2016; Kim et al., 2017). Additional experiments showed that poly(I:C) treatment promoted increased production of IL-17a within maternal gut T_H17 populations, a systemic elevation in IL-17a in maternal plasma and this increase in IL-17a promotes MIA-associated behavioral and neurodevelopmental abnormalities in offspring (Choi et al., 2016; Kim et al., 2017). In addition to revealing novel mechanisms of neurodevelopmental reprogramming, these studies show that rescue and recapitulation of phenotypes are influenced by vendor-specific microbiota profiles (i.e., Taconic vs. Jax) (Choi et al., 2016; Kim et al., 2017). Further, these results open questions for many areas of neuroscience in which the immune system has been implicated to influence behavior, including rodent models of neurodevelopmental disorders, drug abuse and reward and neurodegeneration. Future large-scale efforts will need to identify vendor-specific microbiota and the extent to which these differences may impact experimental outcomes.

2.3. Sex

Differences between males and females in anatomy, physiology and behavior have been described in nearly all vertebrate species, including humans (Jašarević et al., 2016). Sex differences in the microbiome may be driven by complex interactions between sex chromosome complement, gonadal hormones, metabolism, immune function, and neuroendocrine feedback (Handa et al., 1994; Handa and Weiser, 2014; Klein and Flanagan, 2016; O'Malley et al., 1971; Ober et al., 2008). Indeed, a large-scale analysis of the relationship of sex to gut bacterial diversity in a heterogeneous cohort from the US, UK, Colombia and China demonstrated sex-specific microbiota differences (Cuesta-Zuluaga et al., 2019). In this study, common factors known to impact microbial diversity, such as antibiotic usage and cardiometabolic parameters, did not significantly account for sex difference in gut microbiota (Cuesta-Zuluaga et al., 2019). These observations are paralleled in rodent models, wherein male and female offspring exhibit dynamic and development-specific sex differences in gut microbiome composition and function (Jašarević et al., 2017). One potential explanation for sex differences in gut microbiota composition is that the nutritional and energetic demands of growth, development and reproduction differ between males and females, suggesting that sex-specific shifts in community structure and function may represent an adaptation by which organisms maintain sex differences in physiology and behavior throughout life (Reviewed in Jašarević et al., 2016). Indeed, gut microbiota composition and metabolome profiles are significantly different between male and female mice despite consumption of diets that are identical in nutritional profiles (Bolnick et al., 2014).

While host factors, such as genes and hormones, contribute to sex differences in gut microbiota composition, nutrients and metabolites produced by the gut microbiota play a key role in regulating hormone production and systemic endocrine function (Godfrey and Barker, 2000). Studies in germ-free mice reveal that hormone levels correlate with the presence of microbiota, that microbiota produce and secrete hormones, regulate expression levels of hormones, and respond to hormones (Reviewed in Neuman et al., 2015). The triangular link between microbiota, hormones and sex-specific disease susceptibility was first demonstrated in a non-obesogenic type 1 diabetes (T1D) mouse model (NOD), in which females display higher risk of T1D (Markle et al., 2014, 2013). In this model, male-specific protection is linked to testosterone levels and gonadectomy in males increases T1D risk. Surprisingly, sex differences in T1D risk disappeared when NOD mice were raised under germ-free conditions, suggesting a link between presence of microbiota and testosterone levels, and subsequent T1D susceptibility (Markle et al., 2014, 2013). In a hallmark experiment, pubertal females that received microbiota transplants from adult males showed elevated testosterone levels as well as protection from T1D (Markle et al., 2014, 2013). In parallel, high-resolution sequencing of the gut microbiota and gene expression analysis of the immune compartment showed that hormones and microbiota contribute in an additive manner to sex-specific T1D protection in NOD mice (Yurkovetskiy et al., 2013). Together, these studies establish a direct relationship between the microbiome and the endocrine system, and open new and exciting research questions related to the microbiome within the context of neuroendocrinology.

2.4. Diet

The gut microbiota is a key interface for nutrition, with dietary substrates shaping microbial community composition and function, that, in turn, exert important metabolic consequences on the host (David et al., 2014; Kau et al., 2011). Comparison of twins discordant for obesity identified a core microbial community associated with obesity, and transplantation of these obesity-associated microbiota is sufficient to induce obesity in mice (Ridaura et al., 2013; Turnbaugh et al., 2009a, 2008, 2006). Such studies introduced the concept that it is possible to identify distinct microbial communities that are characteristic of a disease state and transplantation of these communities is sufficient to induce disease. Currently, the gold standard for inducing obesity in mice is administration of a high-fat diet over time (Cani et al., 2007; Everard et al., 2013; Turnbaugh et al., 2006; Warden and Fisler, 2008). Studies investigating the role of gut microbiota in diet-induced obesity typically compare mice fed a refined high-fat diet to mice fed a vivarium-provided chow diet (Warden and Fisler, 2008). Chow diet formulations are not standardized, and the nutritional composition differs significantly from refined diets, chief among them being that chow diets contain a large proportion of dietary soluble fiber from unrefined cereals and legumes that is absent from refined diet formulations (Ricci, 2013). The importance of fiber source in microbiota-oriented studies is further supported by a recent comparison of mice consuming either chow diet or refined low-fat diet showing increased adiposity in mice fed a refined low-fat diet relative to chow diet fed mice (Chassaing et al., 2015). To more directly investigate the contribution of dietary fat to obesity, another study examined energy harvest and glucose tolerance in mice fed either a chow diet, refined

low-fat diet, or a refined high-fat diet (Dalby et al., 2017). The chow diet was formulated from unrefined ingredients, while the refined diets were both formulated using identical nutritionally defined and purified ingredients (Dalby et al., 2017). The refined diets contained 5% dietary fiber as cellulose, while the chow diet contained 15% dietary fiber as complex plant polysaccharides (Dalby et al., 2017; Ricci, 2013). Consistent with previous studies, mice fed a high-fat diet showed increased body weight, body fat and higher fasting blood glucose relative to mice on the other two diets (Dalby et al., 2017). Surprisingly, mice on either low or high fat refined diet showed parallel changes in microbiota composition relative to chow-fed diet mice (Dalby et al., 2017). These results demonstrating an uncoupling between high-fat diet consumption, gut microbiota, body fat, and glucose intolerance are important to consider in light of reports showing a role for microbiota in diet-induced obesity (Bäckhed et al., 2004; Dalby et al., 2017; Sonnenburg et al., 2016). Further, addition of the fermentable fiber inulin into a refined high-fat diet protects mice against diet-induced obesity and metabolic syndrome, further highlighting the importance of considering fiber source in dietary manipulation studies (Zou et al., 2018).

While the studies outlined above have focused on metabolic outcomes in adult male rodents, the results highlight important consideration for studies examining the impact of maternal diet and microbiome during pregnancy on lasting offspring outcomes. Maternal dietary intervention studies in rodents have shown that consumption of a high-fat diet is associated with changes to maternal gut microbiota composition and microbial metabolic pathways involved in lipid and glucose metabolism over the course of pregnancy (Gohir et al., 2015). However, studies have predominantly compared animals consuming a refined diet to chow diet-fed animals as the control group, making it difficult to determine the contribution of fat, fiber, or both on associations between maternal diet, gut microbiota composition and offspring outcomes.

Taken together, we hope this brief overview of methodological considerations for studying the microbiome within a neuroscience context will stimulate more microbiota-oriented experiments among neuroscientists. As discussed above, microbial community structure, composition and function are regulated by environmental factors interacting at multiple levels, which itself may influence neurobehavioral outcomes in a manner that is independent of experimental treatment effects. Within this context and important caveats in mind, we review the prenatal and postnatal contributions of the maternal microbiome on offspring brain development.

3. Microbial origins of offspring health

Microbial communities exhibit unique structures based on body habitat that are dynamically regulated by environmental factors in body site-specific ways (Caporaso et al., 2011; Ding and Schloss, 2014). A number of excellent resources are available that discuss human microbial communities of the skin, mouth, gut, and vagina that are outside of the purview of the current review (Dewhirst et al., 2010; Donaldson et al., 2015; Grice and Segre, 2011; Ma et al., 2012). In proceeding sections, we will discuss the structure and function of maternal gut and vaginal microbial communities, and the impact of these communities on maternal and offspring health outcomes.

3.1. The role of the maternal gut microbiota on prenatal development

The role of maternal immunity, metabolism and nutritional status in fetal programming has been the focus of intense study for nearly a century (Bowlby, 1951). Nutrients, gases and metabolites cross the placenta through numerous diffusion and transport processes and enter fetal circulation (Nugent and Bale, 2015). Fetal nutrient requirements change over the course of pregnancy, and pregnant women undergo dynamic metabolic adaptations to meet these demands (Nugent and Bale, 2015). During the first two-thirds of pregnancy when fetal growth is very limited, the mother is in an anabolic state, which is characterized by hyperphagia, lipogenesis, and accumulation of fat stores (Lain and Catalano, 2007). During the last third of pregnancy when fetal growth is rapid, maternal metabolism shifts into a catabolic state that is characterized by an increased basal metabolic rate, enhanced transfer of nutrients, ketogenesis, gluconeogenesis and breakdown of lipid stores (Lain and Catalano, 2007). These metabolic adaptations are essential for the normal development of nutritionally-demanding tissues such as the fetal brain (Lain and Catalano, 2007). Early stages of central nervous system development, including neural migration and synaptogenesis, occur during the anabolic phase of pregnancy where rapid shifts in nutritional availability may impact these processes (Lain and Catalano, 2007). Other critical neurodevelopmental events, such as myelination and formation of synapses begin to occur as the mother transitions into a catabolic state, thereby providing the necessary influx of nutrients and metabolites to support these processes (Georgieff, 2007). Moreover, the developmental trajectories differ between brain regions and require careful orchestration such that nutrients are prioritized to circuits undergoing active development over brain regions that have already been established. The possibility of nutritional partitioning between brain regions may also suggest that actively developing and established circuits exhibit distinct metabolic signatures (Georgieff, 2007). The hypothalamus, the critical regulator of neuroendocrine function and whole-body homeostasis, begins to develop late in gestation and exhibits extreme sensitivity to maternal nutrient availability (Bouret, 2010; Burbridge et al., 2016). Perturbations, such as stress or immune activation, disrupt the tight coordination between fetal demand and maternal availability, rendering the developing hypothalamus particularly sensitive to programming by maternal adversity.

As the central regulator of immunity and metabolism, the intestinal microbiota has the capacity to modulate essentially every aspect of metabolism and nutritional physiology of pregnancy (Koren et al., 2012; Neuman and Koren, 2017; Nuriel-Ohayon et al., 2016). The tremendous genetic repertoire of the microbiome provides extensive metabolic, immunological and endocrine potential otherwise unavailable to the host (Qin et al., 2010). With respect to metabolism, the gut microbiota harvest energy substrates from the diet by digesting and fermenting complex carbohydrates to synthesize short chain fatty acids and production of amino acids, Vitamin K, and B-group vitamins (LeBlanc et al., 2013). The growing literature of the microbiome and metabolism requires a critical reappraisal of maternal metabolic adaptation to pregnancy and fetal programming within the context the gut microbiome (Gohir et al., 2015; Koren et al., 2012; Ma et al., 2014). In humans, maternal gut bacterial load increases over the course of pregnancy, and there is a significant change in gut microbiota composition from the first to the third trimester of pregnancy (Koren et al., 2012). Late gestation is characterized by increased abundance of bacterial phyla *Actinobacteria* and *Proteobacteria* that are associated with systemic inflammation (Koren et al., 2012). Consistently, germ-free mice inoculated with third trimester microbiota, but not first trimester microbiota, showed increased inflammation and adiposity (Koren et al., 2012). While these studies may suggest that the significant remodeling of the maternal gut microbiota during the first and third trimester parallels the metabolic adaptations of pregnancy, more work is required to identify the mechanistic links between the gut microbiome, metabolism and offspring development during pregnancy.

Environmental perturbations may also exert lasting effects on the maternal gut microbiota in humans. Women with a history of adverse childhood experiences (ACEs), such as neglect, abuse or chronic household dysfunction show higher risk for impaired immune function, dysregulated hypothalamic pituitary adrenal (HPA) stress axis response, obstetric complications and offspring outcomes (reviewed in Hantsoo et al., 2019). History of multiple ACEs was associated with changes to gut microbiota composition during pregnancy, and such changes predict inflammatory and glucocorticoid response to acute

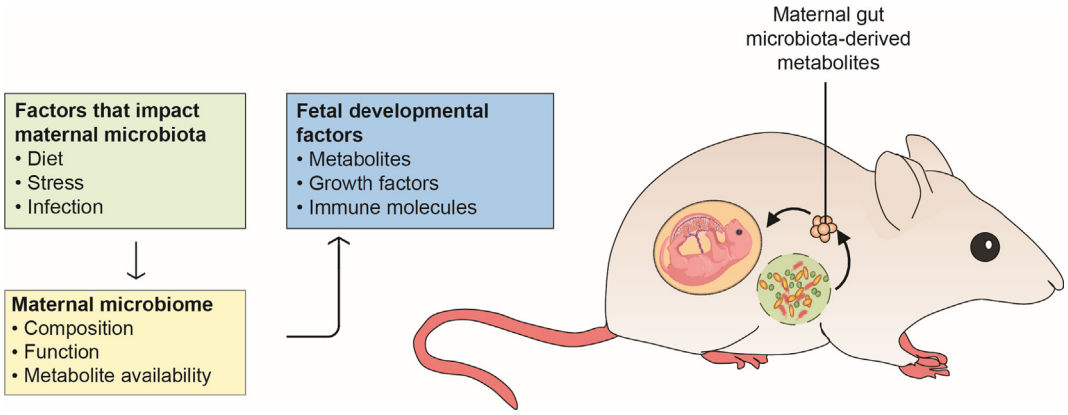

Fig. 2. The role of the maternal gut microbiome on prenatal development. The maternal gut microbiome shifts in composition and function to meet the energetic demand of developing offspring. Maternal exposures, such as diet, stress and infection, may alter maternal gut microbiota composition, function and availability of microbiota-derived metabolites during pregnancy. In turn, alterations in the availability of microbiota-derived metabolites may exert programmatic effects on the placenta and the fetal compartment.

stress during pregnancy (Hantsoo et al., 2019). While these results provide an important association between childhood adversity, maternal gut microbiota and inflammation during pregnancy, additional work is needed to understand how these factors, if at all, contribute to offspring outcomes.

Rodent studies support a mechanistic role of maternal gut microbiota on offspring immune development. In an important proof-of-concept experiment, germ-free pregnant females were inoculated with *E. coli* HA 107, a strain that is incapable of replicating *in vivo* and permits pregnant females to return to germ-free status (De Agüero et al., 2016). Germ-free pups born to transiently colonized dams exhibit distinct gene expression patterns in the intestinal mucosa and increased numbers of type 3 innate lymphoid cells compared with control pups (De Agüero et al., 2016). Isotope labeling of *E. coli* HA 107 showed substantial transfer of molecules from the labelled strain in the placenta and fetal circulation, providing the first evidence of microbiota-derived molecules entering fetal circulation (De Agüero et al., 2016). Similarly, the absence of a microbiome in germ-free mice exhibited temporal, developmental, maturational and sex-specific effects on chromatin accessibility and transcriptome of microglia, the resident macrophage in the brain (Thion et al., 2018).

While these studies demonstrate that a complete absence of microbiota regulate key aspects of peripheral and central immunity, recent efforts have started to investigate the extent to which perturbations to the maternal microbiome contribute to offspring neurodevelopment. Exposure to the synthetic molecule poly(I:C) to mimic viral infection stimulates an immune response in pregnant mice that is associated with neurodevelopmental and behavioral changes in offspring (Choi et al., 2016; Kim et al., 2017). Maternal immune activation during pregnancy was associated with systemic elevation in IL-17a in maternal plasma and this increase in IL-17a promotes MIA-associated behavioral and neurodevelopmental abnormalities in offspring (Choi et al., 2016; Kim et al., 2017). Increased levels of IL-17A was dependent on expansion by T_H17 cells in the gut and on the presence of segmented filamentous bacteria (SFB), a commensal bacterium common within the mouse ileum and cecum (Ivanov et al., 2009; Choi et al., 2016; Kim et al., 2017). Mice lacking SFB failed to exhibit expansion of T_H17 cells and IL-17A secretion (Choi et al., 2016; Kim et al., 2017). Further, absence of SFB prevented maternal immune activation-associated secretion of IL-17A and protected offspring from neurodevelopmental reprogramming and behavioral dysfunction, providing the first evidence that the presence of a specific bacteria in the maternal gut is required for fetal programming of lasting outcomes (Choi et al., 2016; Kim et al., 2017).

Moreover, given the presence maternally microbiota-derived substrates in fetal circulation, it is tempting to speculate on their functional consequence and putative mechanisms related to neurodevelopment. Bacterial fermentation end-products, including short chain fatty acids (SCFAs), function through a variety of properties: (1) fuel for mitochondrial production of energy, (2) modification of histone lysine residues by propionylation and butyrylation, (3) inhibition of histone deacetylase activity, and (4) signaling through G protein-coupled receptors (Arpaia et al., 2013; Chang et al., 2014; Davie, 2003; Hooper et al., 2012; Li et al., 2018; Littman and Pamer, 2011; Steliou et al., 2012). While metabolism and immunity in adult animals are regulated through these diverse mechanisms, the possibility that maternal gut microbiota-derived metabolites act via similar mechanisms in offspring should be further explored. This notion is supported by recent observations that synthesis of maternal SCFAs increases over the course of pregnancy and this increase was necessary to promote differentiation of regulatory T cells in the thymus of offspring. As discussed above, De Agüero and colleagues showed that monocolonization with *E. coli* HA 107 resulted in hundreds of microbially-derived compounds in fetal circulation, suggesting that our knowledge on the quantity and diversity of maternal gut microbiota-derived metabolites in fetal circulation is likely an underestimate (De Agüero et al., 2016). Thus, establishing a direct relationship between maternal gut microbiota, maternal gut microbiota-derived metabolites and offspring development opens exciting new avenues for future research (Fig. 2).

3.2. The role of the vaginal microbiota on offspring outcomes

Culture-dependent studies have suggested for decades that lactobacilli are the primary constituents of the human vaginal microbiota (Hay et al., 1992). More recent culture-independent studies in women demonstrated that vaginal communities are dominated by a single *Lactobacillus* species or a polymicrobial mixture of strict and facultative anaerobes (Gajer et al., 2012; Ma et al., 2012; Ravel et al., 2011; Zhou et al., 2007). Human vaginal communities are now classified into five community state types (CSTs). CST I, II, III and V are dominated by *L. crispatus*, *L. gasseri*, *L. iners*, and *L. jensenii*, respectively (Gajer et al., 2012; Ma et al., 2012; Ravel et al., 2011; Zhou et al., 2007). CST IV is characterized by higher proportions of strictly anaerobic bacteria including *Prevotella, Dialister, Atopobium, Gardnerella, Megasphaera, Peptoniphilus, Sneathia, Eggerthella, Aerococcus, Finegoldia*, and *Mobiluncus* (Gajer et al., 2012; Ma et al., 2012; Ravel et al., 2011; Zhou et al., 2007). As a result, a key signature of CST IV is a higher community diversity and evenness due to the absence of dominant species (Gajer et al., 2012; Ma et al., 2012; Ravel et al., 2011; Zhou et al., 2007). Subsequent examination of CST IV has revealed two distinct sub-

clustered within this community type, CST IV-A and CST IV-B (Romero et al., 2014b, 2014a). Subgroup IV-A is categorized by a moderate proportion of *L. iners* and strict anaerobes, while CST IV-B contains species associated with bacterial vaginosis (Anahtar et al., 2018). The proportion of each CST varies by physiological factors, such as vaginal pH, and population factors, such as ethnicity (Ravel et al., 2011).

The composition of human vaginal microbiota is under the control of environmental, diurnal and hormonal patterns (Anahtar et al., 2018). Longitudinal studies have shown that human vaginal microbial communities can transition in and out of community state types, and the length of time spent in a particular CST exhibits high individual variability (Anahtar et al., 2018). Currently, these individual differences in community stability are driven by hygiene practices, history of infections, contraction of sexually transmitted pathogens, presence of *Gardnerella*, and gonadal hormone levels across the menstrual cycle (Anahtar et al., 2018). The influence of additional environmental factors, such as stress and diet, on human vaginal community stability is less understood. Although chronic stress has been associated with bacterial vaginosis, menstrual cycle irregularity and amenorrhea, the interaction between stress, menstrual dysfunction and vaginal community stability remain unexplored (Culhane et al., 2002, 2001). Given that community instability is associated with adverse obstetric outcomes, the possibility that stress impacts community state type stability is a particularly relevant public health questions worth investigating (Anahtar et al., 2018).

Pregnancy exerts unique ecological pressures on vaginal microbiota in humans (Anahtar et al., 2018). Stability of vaginal microbiota during pregnancy depends on the CST prior to pregnancy: *Lactobacillus*-dominated CSTs are more stable across gestation, while CST IV is less stable and exhibits higher rates of transition of alternate CSTs (Anahtar et al., 2018). Circulating estrogens and progesterone are a major contributor to the increased dominance of lactobacilli as gestation progresses (Anahtar et al., 2018). This estrogen-mediated dominance of *Lactobacillus* species may confer some protection against infection and negative pregnancy outcomes. It is important to emphasize that in contrast to the gut microbiota, high diversity in the vagina is associated with reduced antimicrobial defense mechanisms and negative pregnancy outcomes (Elovitz et al., 2019). Loss of *Lactobacillus* during pregnancy and transitions to CST IV subgroups are associated with preterm birth, preterm premature rupture of membranes, and bacterial vaginosis, which is further associated with miscarriage (Callahan et al., 2017; DiGiulio et al., 2015; Hyman et al., 2014). However, the strength of these associations is modulated by population level factors and local immune changes to barrier defense (Callahan et al., 2017; Elovitz et al., 2019). Moreover, much remains to be learned about the interaction between environmental factors, CSTs, vaginal epithelial cells and the immune system during pregnancy, which may be facilitated through the use of model organisms (Vrbanac et al., 2018). Although chronic stress during pregnancy is associated with bacterial vaginosis and the CST IV-B subgroup contains bacterial vaginosis species, the direct interaction between these factors remains unexplored (Romero et al., 2014b). Future research focused on these complex interactions to identify predictive microbial signatures in vaginal microbiota related to chronic stress risk or resilience may provide novel strategies to restore a protective vaginal microbiota.

Taken together, our current understanding is that the vaginal microbiota cluster into five community state types and stability of these communities is modulated by population-level, environmental, hormonal and diurnal patterns. Transition in and out of community state types is common, but the factors that influence community instability and their downstream consequences are not fully understood. The maternal vaginal microbiota is a transient source for early-in-life gut colonization, however, the possibility that transient colonization by distinct community state types may impact aspects of offspring development remains unknown.

3.3. The specific importance of vertical transmission of maternal microbiota in postnatal development

Perturbations that occur preconception or during pregnancy that impact vaginal microbiota community dynamics may influence the microbiota transmitted from mother to offspring at birth. Culture-dependent studies proposed that maternal microbiota represent a crucial reservoir for the early acquisition of a microbiome in the newborn gut (Mackie et al., 1999). Further, the extent to which maternal microbiota colonize the newborn is influenced by several factors including gestational age at birth, length of gestation, mode of delivery, maternal antibiotic use, feeding method, and early intimate contact with the mother (Bokulich et al., 2016; La Rosa et al., 2014; Schwiertz et al., 2003; Stearns et al., 2017; Stewart et al., 2018; Wampach et al., 2018). However, until recently, the exact maternal sources of microbial transmission were not fully understood. Evidence from the first 16S rRNA marker gene sequencing to interrogate this question demonstrated overlapping community composition between newborn gut microbiota and maternal vaginal microbiota, but not in that of cesarean delivered offspring, suggested that the maternal vaginal microbiota is a reservoir for the pioneer community that initially colonizes the newborn gut (Dominguez-Bello et al., 2010). A more recent metagenomic study longitudinally sampled mother-infant pairs across multiple body sites (i.e., vagina, skin, breast milk, oral cavity, and feces) from birth to 4 months postpartum, and applied a novel computational profiling approach that enables tracking of mother-to-infant strain transmission and strain-level assembly in the infant gut (Ferretti et al., 2018). This approach revealed that maternal vaginal and skin strains transiently colonize the infant gut, followed by replacement by maternal gut strains that remained more persistent in the infant gut across development (Ferretti et al., 2018). Further, maternally transmitted strains were more likely to adapt and persist in the infant gut than non-maternally acquired strains, supporting the concept that selective pressures within the neonatal gut may favor maternally acquired microbes, and further reinforces the importance of maternal-to-infant vertical transmission (Ferretti et al., 2018).

Acquisition of maternal microbiota has been associated with various developmental milestones in the neonate, such as innate immune development and metabolism, and the mechanisms by which maternal microbial signals drive these processes are beginning to emerge (Mueller et al., 2015). To date, the effects of disrupting mother-to-infant transmission have been largely studied within the context of birth mode by comparing outcomes in vaginally delivered or cesarean delivered neonates. Broad compositional differences have been observed between vaginal and cesarean delivered neonates within the first few days of life that resolve over time (Dominguez-Bello et al., 2010). Alterations in strains transferred to cesarean delivered neonates is associated with underrepresentation of microbial functional pathways, such as lipopolysaccharide (LPS) biosynthetic pathways (Wampach et al., 2018). LPS is a surface membrane component of Gram-negative bacteria and recognized by toll-like receptor 4 (TLR4) on the membranes of intestinal epithelial cells that stimulate components of the immune system (Wampach et al., 2018). To assess the immunostimulatory potential of maternal microbiota transferred to infants, a recent study showed that fecal LPS isolated from 3-day-old vaginally delivered neonates induced higher levels of the cytokines, TNF-α and IL-18, in monocyte-derived dendritic cells compared with fecal LPS from 3-day-old cesarean delivered neonates (Wampach et al., 2018). The possibility that microbiota immunogenicity during the first few days to weeks of life could significantly shape the innate and adaptive immune system is supported by recent observations that stably low microbiota diversity in infants was associated with higher circulating activated T cell populations and lower circulating basophil, neutrophil and plasmacytoid dendritic cell populations (Lee et al., 2019; Olin et al., 2018).

Although the exact mechanisms by which microbial signals and downstream effectors regulate the functional development of the

immune system remain to be identified in humans, studies in rodent models provide some insight. In mice, the predominant taxa that colonize the mouse neonatal gut belongs to the class Gammaproteobacteria (Deshmukh et al., 2014; Jašarević et al., 2017; Mirpuri et al., 2013). Within 3 days following birth, Gammaproteobacteria colonization activates a TLR4 signaling cascade to increase production of the cytokine, IL-17A, by type 3 innate lymphoid cells in the neonate gut. Upregulation of IL-17A triggers an increase in plasma G-CSF to induce production of granulocytes in the bone marrow (Deshmukh et al., 2014). In addition, the increased production of IL-17A in the neonate gut stimulates the egress of neutrophils from the bone marrow and into circulation (Deshmukh et al., 2014). This microbiota-mediated influx of neutrophils into the bloodstream protects neonates from systemic infection by the blood-borne pathogens *Escherichia coli* K1 and *Klebsiella peumoniae* (Deshmukh et al., 2014). However, excessive neutrophil infiltration may lead to chronic inflammation and permanent tissue damage, thereby requiring additional checkpoint mechanisms (Deshmukh et al., 2014). One potential mechanism by which neonatal colonization may restrain excessive immune activation is through the induction of microRNA-146a in intestinal epithelial cells (Chassin et al., 2010). Sustained levels of microRNA-146a function to proteolytically degrade the TLR4 signaling molecule IRAK1, a potent activator of proinflammatory signaling cascades (Chassin et al., 2010). This translational repression of IRAK1 resulted in gene expression patterns involved in cell survival and metabolism, immune tolerance, and protection from microbial-induced epithelial damage in neonates (Chassin et al., 2010). Conversely, preventing vertical transmission of maternal microbiota to neonates prevents colonization by Gammaproteobacteria and all of the downstream effector processes to ultimately render neonates susceptible to mucosal damage and infection (Deshmukh et al., 2014). Taken together, these studies in humans and rodent models highlight the importance of maternally-acquired microbiota in the functional development of the neonate immune system may help explain why maternally transmitted strains are also more likely to adapt and persist in the infant gut than non-maternally acquired strains.

Given that the maternal communities that are vertically transmitted to offspring show high degree of inter-individual variability, it poses the question of what factors explain this inherent variability and whether variability in maternally acquired microbiota influence phenotypic outcomes in offspring (Fig. 3). Stress during pregnancy has been identified as one component that may influence the composition of microbiota transferred to offspring at birth (Bailey and Coe, 1999; Jašarević et al., 2015; Zijlmans et al., 2015). Indeed, pregnant mice exposed to stress during the first week of pregnancy show alterations in the composition of the gut and vaginal microbiota (Jašarević et al., 2017, 2015). Specifically, stress decreased *Lactobacillus* abundance, an effect that was independent of total bacterial load and was associated with a parallel reduction of *Lactobacillus* abundance in the postnatal day (PN) 2 colon of exposed offspring compared with control offspring (Jašarević et al., 2017, 2015). These compositional changes in the colonizing microbiota were associated with changes to metabolite profiles in the periphery and the PN2 brain (Jašarević et al., 2017, 2015).

One particular challenge in demonstrating a mechanistic contribution of the maternal microbiota on offspring health outcomes is that any environmental insults that occur during pregnancy are equally likely to impact maternal microbiota and the developing fetus. In other words, offspring from a stress-exposed dam will be exposed to stress *in utero* and colonized by stress-altered microbiota. As such, this approach does not provide insight on the specific role of the maternal microbiota on key aspects of the prenatal stress phenotype. Thus, the direct effect of stress-altered maternal microbiota on offspring phenotype can be addressed by delivering control and prenatal stress exposed mouse pups by C-section and colonizing newborn pups with microbiota from either stress-exposed or control dams (Jašarević et al., 2018). Indeed, transplantation of vaginal microbiota from stress-exposed females into naïve offspring recapitulated key phenotypes that are observed in prenatal stress exposed offspring, including altered microbiota composition, body weight changes and increased corticosterone response to an acute stressor (Jašarević et al., 2018). Surprisingly, prenatal-stress exposed offspring transplanted with a vaginal sample from control dams failed to rescue of prenatal stress effects on body weight and corticosterone response to acute stress (Jašarević et al., 2018). This inability to rescue the prenatal stress phenotype was related to transcriptomic reprogramming of the fetal intestine prior to birth (Jašarević et al., 2018). In parallel with a recent report, these data may suggest that prenatal environmental perturbations also influence the fetal gut in a manner that determines which pioneer bacterial communities to gain entry, establish residence, and interact with the developing immune system (De Agüero et al., 2016). Currently, there are no studies available that have systematically assessed the role of maternal adversity during pregnancy, maternal microbiota, fetal reprogramming and early-in-life microbiota dynamics in humans but more work in this growing area is anticipated.

Given the dynamic restructuring of the offspring microbiota that occurs during the first 1000 days (Subramanian et al., 2015), it is reasonable to question whether early-in-life alterations to microbiota produce enduring changes. Recent efforts have tracked microbiota patterns in children across development and showed that assembly of gut microbial communities results from repeated cycles of colonization, largely driven by age-associated events such as weaning. Surprisingly, the assembly of microbial communities is highly correlated with chronological age, where age-discriminatory microbiota identified in one model could predict the chronological ages of children from a separate cohort (Subramanian et al., 2014). This approach showed that if the gut microbiota of a child resembles that of a 6-month-old when they are actually 18-months-old, then the gut microbiota is immature and has fallen out of sync with host chronological age. When applied to a cohort of severely malnourished children living in the Mirpur urban slum of Dhaka, Bangladesh, they showed severe gut microbiota immaturity could not be reversed with dietary interventions (Subramanian et al., 2014). These findings parallel what has been previously observed in studies of malnutrition in humanized mouse model (Smith et al., 2013). In addition, recent rodent studies have applied these metrics to show that maternal stress and antibiotic exposure disrupts assembly of microbiota where maternal stress accelerates microbiota assembly and early-life antibiotic exposure delays microbiota assembly (Jašarević et al., 2017; Nobel et al., 2015) Together, these studies highlight the necessity of additional longitudinal experiments that explicitly capture the dynamic nature of microbial assembly, development and lasting phenotypic outcomes.

4. Conclusion

Microbiome research is slowly becoming incorporated within the neurosciences, and we envision this trend will continue to grow. Seminal reports now exist demonstrating the contribution of microbial communities in various aspects of neurodevelopment and behavioral function, requiring a reappraisal of the role of the maternal milieu in neurodevelopment within the context of the microbiome. We anticipate inclusion of the maternal microbiome to uncover novel mechanisms involved in immune, metabolic and physiologic programming and subsequent risk or resilience to disorders later in life. In this review, we propose that offspring development may occur via the maternal microbiota through two overlapping processes. First, maternal gut microbiota composition and function during pregnancy may impact the available pool of microbe derived metabolites and substrates that are necessary for normal prenatal growth and development. Maternal gut microbiota-derived metabolites may influence brain development through various processes, including facilitating mitochondrial production of energy, chromatin remodeling, signaling through G protein-coupled receptors, or through novel mechanisms that remain to be

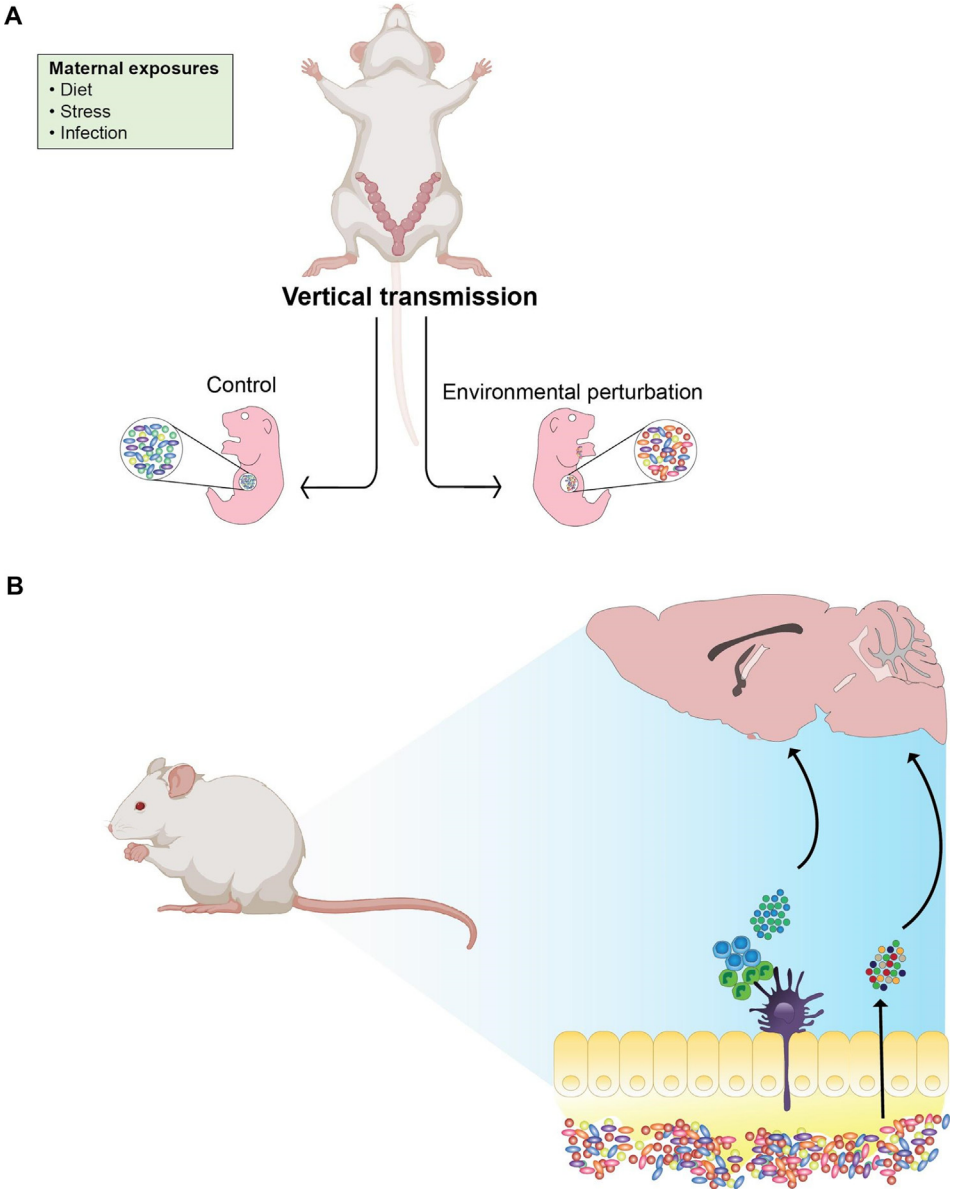

Fig. 3. The role of vertical transmission of maternal microbiota on postnatal development. Colonization by maternal microbiota at birth plays a key role in immune education, metabolism and neurodevelopment. (A) Maternal exposure, such as diet, stress and infection, may alter the maternal vaginal microbiota transmitted to offspring and subsequently influence immunity, metabolism and brain development. (B) Vertically transmitted maternal vaginal microbiota influences local and systemic immune development and metabolism. Colonization stimulates innate immune cells, such as neutrophils, to infiltrate peripheral and central tissues. Moreover, the colonizing microbiota also provide critical metabolic support in synthesizing and metabolizing key metabolites necessary for postnatal growth. These immune and metabolic changes may represent key drivers of enduring transcriptional changes in these brain regions, such as the hypothalamus.

characterized. Identification of all possible microbial metabolites of maternal origin in fetal circulation remains a challenge, and technical advances will be necessary to better understand the role of maternal microbiota and its metabolites on fetal development, including the brain. Second, transmission of maternal microbiota at birth contribute to the metabolism, immunity and nervous system of offspring that may exert lasting health outcomes. In rodent models, perturbations to maternal microbiota communities influence colonization patterns of the neonate and exert lasting outcomes in offspring. Additional work in is needed to determine the neonate's response to colonization at birth and the mechanism by which different assemblages of microbiota shape immunity, metabolism and neurodevelopment. Further, additional techniques and methods are needed in conventionalized mice to manipulate microbiota at distinct stages of development to assess the contribution of microbiota early in life and durable health outcomes. Although we are in the early days of understanding the contribution of maternal microbiota and microbial metabolites to offspring development, it has the potential to offer a novel translational research agenda to understand maternal-fetal health.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yfrne.2019.100797.

References

Abdel-Haq, R., Schlachetzki, J.C.M., Glass, C.K., Mazmanian, S.K., 2019. Microbiome–microglia connections via the gut–brain axis. J. Exp. Med. https://doi.org/10.1084/jem.20180794.

Anahtar, M.N., Gootenberg, D.B., Mitchell, C.M., Kwon, D.S., 2018. Cervicovaginal microbiota and reproductive health: the virtue of simplicity. Cell Host Microbe. https://

doi.org/10.1016/j.chom.2018.01.013.
Arpaia, N., Campbell, C., Fan, X., Dikiy, S., Van Der Veeken, J., Deroos, P., Liu, H., Cross, J.R., Pfeffer, K., Coffer, P.J., Rudensky, A.Y., 2013. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature. https://doi.org/10.1038/nature12726.
Asnicar, F., Manara, S., Zolfo, M., Truong, D.T., Scholz, M., Armanini, F., Ferretti, P., Gorfer, V., Pedrotti, A., Tett, A., Segata, N., 2017. Studying vertical microbiome transmission from mothers to infants by strain-level metagenomic profiling. mSystems. https://doi.org/10.1128/msystems.00164-16.
Bäckhed, F., Ding, H., Wang, T., Hooper, L.V., Koh, G.Y., Nagy, A., Semenkovich, C.F., Gordon, J.I., 2004. The gut microbiota as an environmental factor that regulates fat storage. Proc. Natl. Acad. Sci. USA. https://doi.org/10.1073/pnas.0407076101.
Bailey, M.T., Coe, C.L., 1999. Maternal separaseparation disrupts the integrity of the intestinal microflora in infant rhesus monkeys. Dev. Psychobiol. https://doi.org/10.1002/(SICI)1098-2302(199909)35:2<146::AID-DEV7>3.0.CO;2-G.
Bale, T.L., 2015. Epigenetic and transgenerational reprogramming of brain development. Nat. Rev. Neurosci. https://doi.org/10.1038/nrn3818.
Bastiaanssen, T.F.S., Cowan, C.S.M., Claesson, M.J., Dinan, T.G., Cryan, J.F., 2018. Making sense of ··· the microbiome in psychiatry. Int. J. Neuropsychopharmacol. https://doi.org/10.1093/ijnp/pyy067.
Bevins, C.L., Salzman, N.H., 2011. Paneth cells, antimicrobial peptides and maintenance of intestinal homeostasis. Nat. Rev. Microbiol. https://doi.org/10.1038/nrmicro2546.
Blanton, L.V., Charbonneau, M.R., Salih, T., Barratt, M.J., Venkatesh, S., Ilkaveya, O., Subramanian, S., Manary, M.J., Trehan, I., Jorgensen, J.M., Fan, Y.M., Henrissat, B., Leyn, S.A., Rodionov, D.A., Osterman, A.L., Maleta, K.M., Newgard, C.B., Ashorn, P., Dewey, K.G., Gordon, J.I., 2016. Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children. Science (80-.). https://doi.org/10.1126/science.aad3311.
Bloom, S.M., Bijanki, V.N., Nava, G.M., Sun, L., Malvin, N.P., Donermeyer, D.L., Dunne, W.M., Allen, P.M., Stappenbeck, T.S., 2011. Commensal Bacteroides species induce colitis in host-genotype-specific fashion in a mouse model of inflammatory bowel disease. Cell Host Microbe. https://doi.org/10.1016/j.chom.2011.04.009.
Bokulich, N.A., Chung, J., Battaglia, T., Henderson, N., Jay, M., Li, H., Lieber, A.D., Wu, F., Perez-Perez, G.I., Chen, Y., Schweizer, W., Zheng, X., Contreras, M., Dominguez-Bello, M.G., Blaser, M.J., 2016. Antibiotics, birth mode, and diet shape microbiome maturation during early life. Sci. Transl. Med. https://doi.org/10.1126/scitranslmed.aad7121.
Bolnick, D.I., Snowberg, L.K., Hirsch, P.E., Lauber, C.L., Org, E., Parks, B., Lusis, A.J., Knight, R., Caporaso, J.G., Svanbäck, R., 2014. Individual diet has sex-dependent effects on vertebrate gut microbiota. Nat. Commun. https://doi.org/10.1038/ncomms5500.
Boullier, M., Blair, M., 2018. Adverse childhood experiences. Paediatr. Child Heal. (United Kingdom). https://doi.org/10.1016/j.paed.2017.12.008.
Bouret, S.G., 2010. Role of early hormonal and nutritional experiences in shaping feeding behavior and hypothalamic development. J. Nutr. https://doi.org/10.3945/jn.109.112433.
Bowlby, J., 1951. Maternal Care and Mental Health. Bull, World Health Organ.
Bravo, J.A., Forsythe, P., Chew, M.V., Escaravage, E., Savignac, H.M., Dinan, T.G., Bienenstock, J., Cryan, J.F., 2011. Ingestion of *Lactobacillus* strain regulates emotional behaviors and central GABA receptor expression in a mouse via the vagus nerve. PNAS. https://doi.org/10.1073/pnas.1102999108.
Burbridge, S., Stewart, I., Placzek, M., 2016. Development of the neuroendocrine hypothalamus. Compr. Physiol. https://doi.org/10.1002/cphy.c150023.
Byndloss, M.X., Pernitzsch, S.R., Bäumler, A.J., 2018. Healthy hosts rule within: ecological forces shaping the gut microbiota. Mucosal Immunol. https://doi.org/10.1038/s41385-018-0010-y.
Callahan, B.J., DiGiulio, D.B., Goltsman, D.S.A., Sun, C.L., Costello, E.K., Jeganathan, P., Biggio, J.R., Wong, R.J., Druzin, M.L., Shaw, G.M., Stevenson, D.K., Holmes, S.P., Relman, D.A., 2017. Replication and refinement of a vaginal microbial signature of preterm birth in two racially distinct cohorts of US women. Proc. Natl. Acad. Sci. https://doi.org/10.1073/pnas.1705899114.
Cani, P.D., Amar, J., Iglesias, M.A., Poggi, M., Knauf, C., Bastelica, D., Neyrinck, A.M., Fava, F., Tuohy, K.M., Chabo, C., Waget, A., Delmée, E., Cousin, B., Sulpice, T., Chamontin, B., Ferrières, J., Tanti, J.-F., Gibson, G.R., Casteilla, L., Delzenne, N.M., Alessi, M.C., Burcelin, R., 2007. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. https://doi.org/10.2337/db06-1491.
Caporaso, J.G., Lauber, C.L., Costello, E.K., Berg-Lyons, D., Gonzalez, A., Stombaugh, J., Knights, D., Gajer, P., Ravel, J., Fierer, N., Gordon, J.I., Knight, R., 2011. Moving pictures of the human microbiome. Genome Biol. https://doi.org/10.1186/gb-2011-12-5-r50.
Chang, P.V., Hao, L., Offermanns, S., Medzhitov, R., 2014. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. Proc. Natl. Acad. Sci. https://doi.org/10.1073/pnas.1322269111.
Chassaing, B., Miles-Brown, J., Pellizzon, M., Ulman, E., Ricci, M., Zhang, L., Patterson, A.D., Vijay-Kumar, M., Gewirtz, A.T., 2015. Lack of soluble fiber drives diet-induced adiposity in mice. Am. J. Physiol. Liver Physiol. https://doi.org/10.1152/ajpgi.00172.2015.
Chassin, C., Kocur, M., Pott, J., Duerr, C.U., Gütle, D., Lotz, M., Hornef, M.W., 2010. MiR-146a mediates protective innate immune tolerance in the neonate intestine. Cell Host Microbe. https://doi.org/10.1016/j.chom.2010.09.005.
Choi, G.B., Yim, Y.S., Wong, H., Kim, Sangdoo, Kim, H., Kim, Sangwon V., Hoeffer, C.A., Littman, D.R., Huh, J.R., 2016. The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. Science (80-). https://doi.org/10.1126/science.aad0314.
Cox, L.M., Blaser, M.J., 2015. Antibiotics in early life and obesity. Nat. Rev. Endocrinol. 11, 182–190. https://doi.org/10.1038/nrendo.2014.210.
Cryan, J.F., Dinan, T.G., 2012. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat. Rev. Neurosci. https://doi.org/10.1038/nrn3346.
Cuesta-Zuluaga, J. de la, Kelley, S.T., Chen, Y., Esobar, J.S., Mueller, N.T., Ley, R.E., McDonald, D., Huang, S., Swafford, A.D., Knight, R., Thackray, V., 2019. Age and sex-dependent patterns of gut microbial diversity in human adults. bioRxiv. https://doi.org/10.1101/544270.
Culhane, J.F., Rauh, V., McCollum, K.F., Elo, I.T., Hogan, V., 2002. Exposure to chronic stress and ethnic differences in rates of bacterial vaginosis among pregnant women. Am. J. Obstet. Gynecol. https://doi.org/10.1067/mob.2002.127311.
Culhane, J.F., Rauh, V., McCollum, K.F., Hogan, V.K., Agnew, K., Wadhwa, P.D., 2001. Maternal stress is associated with bacterial vaginosis in human pregnancy. Matern. Child Health J. https://doi.org/10.1023/A:1011305300690.
Dalby, M.J., Ross, A.W., Walker, A.W., Morgan, P.J., 2017. Dietary uncoupling of gut microbiota and energy harvesting from obesity and glucose tolerance in mice. Cell Rep. https://doi.org/10.1016/j.celrep.2017.10.056.
David, L.A., Maurice, C.F., Carmody, R.N., Gootenberg, D.B., Button, J.E., Wolfe, B.E., Ling, A.V., Devlin, A.S., Varma, Y., Fischbach, M.A., Biddinger, S.B., Dutton, R.J., Turnbaugh, P.J., 2014. Diet rapidly and reproducibly alters the human gut microbiome. Nature. https://doi.org/10.1038/nature12820.
Davie, J.R., 2003. Inhibition of histone deacetylase activity by butyrate. J. Nutr. https://doi.org/10.1093/jn/133.7.2485S.
De Agüero, M.G., Ganal-Vonarburg, S.C., Fuhrer, T., Rupp, S., Uchimura, Y., Li, H., Steinert, A., Heikenwalder, M., Hapfelmeier, S., Sauer, U., McCoy, K.D., Macpherson, A.J., 2016. The maternal microbiota drives early postnatal innate immune development. Science (80-). https://doi.org/10.1126/science.aad2571.
Deshmukh, H.S., Liu, Y., Menkiti, O.R., Mei, J., Dai, N., O'Leary, C.E., Oliver, P.M., Kolls, J.K., Weiser, J.N., Worthen, G.S., 2014. The microbiota regulates neutrophil homeostasis and host resistance to *Escherichia coli* K1 sepsis in neonatal mice. Nat. Med. https://doi.org/10.1038/nm.3542.
Dewhirst, F.E., Chen, T., Izard, J., Paster, B.J., Tanner, A.C.R., Yu, W.H., Lakshmanan, A., Wade, W.G., 2010. The human oral microbiome. J. Bacteriol. https://doi.org/10.1128/JB.00542-10.
Diaz Heijtz, R., Wang, S., Anuar, F., Qian, Y., Bjorkholm, B., Samuelsson, A., Hibberd, M.L., Forssverg, H., Pettersson, S., 2011. Normal gut microbiota modulates brain development and behavior. PNAS. https://doi.org/10.1073/pnas.1010529108.
DiGiulio, D.B., Callahan, B.J., McMurdie, P.J., Costello, E.K., Lyell, D.J., Robaczewska, A., Sun, C.L., Goltsman, D.S.A., Wong, R.J., Shaw, G., Stevenson, D.K., Holmes, S.P., Relman, D.A., 2015. Temporal and spatial variation of the human microbiota during pregnancy. Proc. Natl. Acad. Sci. https://doi.org/10.1073/pnas.1502875112.
Ding, T., Schloss, P.D., 2014. Dynamics and associations of microbial community types across the human body. Nature. https://doi.org/10.1038/nature13178.
Dominguez-Bello, M.G., Costello, E.K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N., Knight, R., 2010. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc. Natl. Acad. Sci. USA. https://doi.org/10.1073/pnas.1002601107.
Donaldson, G.P., Lee, S.M., Mazmanian, S.K., 2015. Gut biogeography of the bacterial microbiota. Nat. Rev. Microbiol. https://doi.org/10.1038/nrmicro3552.
Donohoe, D.R., Garge, N., Zhang, X., Sun, W., O'Connell, T.M., Bunger, M.K., Bultman, S.J., 2011. The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. Cell Metab. https://doi.org/10.1016/j.cmet.2011.02.018.
Dozier, M., Bick, J., 2007. Changing caregivers: coping with early adversity. Pediatr. Ann.
Eberl, G., 2015. Addressing the experimental variability associated with the microbiota. Mucosal Immunol. https://doi.org/10.1038/mi.2015.26.
Elovitz, M.A., Gajer, P., Riis, V., Brown, A.G., Humphrys, M.S., Holm, J.B., Ravel, J., 2019. Cervicovaginal microbiota and local immune response modulate the risk of spontaneous preterm delivery. Nat. Commun. https://doi.org/10.1038/s41467-019-09285-9.
Ericsson, A.C., Davis, J.W., Spollen, W., Bivens, N., Givan, S., Hagan, C.E., McIntosh, M., Franklin, C.L., 2015a. Effects of vendor and genetic background on the composition of the fecal microbiota of inbred mice. PLoS ONE. https://doi.org/10.1371/journal.pone.0116704.
Ericsson, A.C., Franklin, C.L., 2015. Manipulating the gut microbiota: methods and challenges. ILAR J. https://doi.org/10.1093/ilar/ilv021.
Ericsson, A.C., Gagliardi, J., Bouhan, D., Spollen, W.G., Givan, S.A., Franklin, C.L., 2018. The influence of caging, bedding, and diet on the composition of the microbiota in different regions of the mouse gut. Sci. Rep. https://doi.org/10.1038/s41598-018-21986-7.
Ericsson, A.C., Akter, S., Hanson, M.M., Busi, S.B., Parker, T.W., Schehr, R.J., Hankins, M.A., Ahner, C.E., Davis, J.W., Franklin, C.L., Amos-Landgraf, J.M., Bryda, E.C., 2015b. Differential susceptibility to colorectal cancer due to naturally occurring gut microbiota. Onctotarget https://doi.org/10.18632/oncotarget.5604.
Erny, D., Hrabě de Angelis, A.L., Jaitin, D., Wieghofer, P., Staszewski, O., David, E., Keren-Shaul, H., Mahlakoiv, T., Jakobshagen, K., Buch, T., Schwierzeck, V., Utermöhlen, O., Chun, E., Garrett, W.S., McCoy, K.D., Diefenbach, A., Staeheli, P., Stecher, B., Amit, I., Prinz, M., 2015. Host microbiota constantly control maturation and function of microglia in the CNS. Nat. Neurosci. 18, 965–977. https://doi.org/10.1038/nn.4030.
Everard, A., Belzer, C., Geurts, L., Ouwerkerk, J.P., Druart, C., Bindels, L.B., Guiot, Y., Derrien, M., Muccioli, G.G., Delzenne, N.M., de Vos, W.M., Cani, P.D., 2013. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. Proc. Natl. Acad. Sci. https://doi.org/10.1073/pnas.1219451110.
Faith, J.J., Ahern, P.P., Ridaura, V.K., Cheng, J., Gordon, J.I., 2014. Identifying gut microbe-host phenotype relationships using combinatorial communities in gnotobiotic mice. Sci. Transl. Med. https://doi.org/10.1126/scitranslmed.3008051.

Faith, J.J., Rey, F.E., O'Donnell, D., Karlsson, M., McNulty, N.P., Kallstrom, G., Goodman, A.L., Gordon, J.I., 2010. Creating and characterizing communities of human gut microbes in gnotobiotic mice. ISME J. https://doi.org/10.1038/ismej.2010.110.

Feehley, T., Plunkett, C.H., Bao, R., Hong, S.M.C., Culleen, E., Belda-Ferre, P., Campbell, E., Aitoro, R., Nocerino, R., Paparo, L., Andrade, J., Antonopoulos, D.A., Canani, R.B., Nagler, C.R., 2019. Healthy infants harbor intestinal bacteria that protect against food allergy. Nat. Med. 25, 448–453. https://doi.org/10.1038/s41591-018-0324-z.

Ferretti, P., Pasolli, E., Tett, A., Asnicar, F., Gorfer, V., Fedi, S., Armanini, F., Truong, D.T., Manara, S., Zolfo, M., Beghini, F., Bertorelli, R., De Sanctis, V., Bariletti, I., Canto, R., Clementi, R., Cologna, M., Crifò, T., Cusumano, G., Gottardi, S., Innamorati, C., Masè, C., Postai, D., Savoi, D., Duranti, S., Lugli, G.A., Mancabelli, L., Turroni, F., Ferrario, C., Milani, C., Mangifesta, M., Anzalone, R., Viappiani, A., Yassour, M., Vlamakis, H., Xavier, R., Collado, C.M., Koren, O., Tateo, S., Soffiati, M., Pedrotti, A., Ventura, M., Huttenhower, C., Bork, P., Segata, N., 2018. Mother-to-infant microbial transmission from different body sites shapes the developing infant gut microbiome. Cell Host Microbe. https://doi.org/10.1016/j.chom.2018.06.005.

Forster, S.C., Kumar, N., Anonye, B.O., Almeida, A., Viciani, E., Stares, M.D., Dunn, M., Mkandawire, T.T., Zhu, A., Shao, Y., Pike, L.J., Louie, T., Browne, H.P., Mitchell, A.L., Neville, B.A., Finn, R.D., Lawley, T.D., 2019. A human gut bacterial genome and culture collection for improved metagenomic analyses. Nat. Biotechnol. https://doi.org/10.1038/s41587-018-0009-7.

Foster, J.A., Rinaman, L., Cryan, J.F., 2017. Stress & the gut-brain axis: regulation by the microbiome. Neurobiol. Stress. https://doi.org/10.1016/j.ynstr.2017.03.001.

Franklin, C.L., Ericsson, A.C., 2017. Microbiota and reproducibility of rodent models. Lab Anim. (NY). https://doi.org/10.1038/laban.1222.

Frost, G., Sleeth, M.L., Sahuri-Arisoylu, M., Lizarbe, B., Cerdan, S., Brody, L., Anastasovska, J., Ghourab, S., Hankir, M., Zhang, S., Carling, D., Swann, J.R., Gibson, G., Viardot, A., Morrison, D., Thomas, E.L., Bell, J.D., 2014. The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. Nat. Commun. 5, 1–11. https://doi.org/10.1038/ncomms4611.

Fung, T.C., Olson, C.A., Hsiao, E.Y., 2017. Interactions between the microbiota, immune and nervous systems in health and disease. Nat. Neurosci. https://doi.org/10.1038/nn.4476.

Funkhouser, L.J., Bordenstein, S.R., 2013. Mom knows best: the universality of maternal microbial transmission. PLOS Biol. 11, e1001631. https://doi.org/10.1371/journal.pbio.1001631.

Gajer, P., Brotman, R.M., Bai, G., Sakamoto, J., Schütte, U.M.E., Zhong, X., Koenig, S.S.K., Fu, L., Ma, Z., Zhou, X., Abdo, Z., Forney, L.J., Ravel, J., 2012. Temporal dynamics of the human vaginal microbiota. Sci. Transl. Med. https://doi.org/10.1126/scitranslmed.3003605.

Gensollen, T., Iyer, S.S., Kasper, D.L., Blumberg, R.S., 2016. How colonization by microbiota in early life shapes the immune system. Science. https://doi.org/10.1126/science.aad9378.

Georgieff, M.K., 2007. Nutrition and the developing brain: Nutrient priorities and measurement. Am. J. Clin. Nutr.

Gilbert, J.A., Blaser, M.J., Caporaso, J.G., Jansson, J.K., Lynch, S.V., Knight, R., 2018. Current understanding of the human microbiome. Nat. Med. https://doi.org/10.1038/nm.4517.

Godfrey, K.M., Barker, D.J.P., 2000. Fetal nutrition and adult disease. Am. J. Clin. Nutr.

Gohir, W., Ratcliffe, E.M., Sloboda, D.M., 2015. Of the bugs that shape us: maternal obesity, the gut microbiome, and long-term disease risk. Pediatr. Res. https://doi.org/10.1038/pr.2014.169.

Goodman, A.L., Kallstrom, G., Faith, J.J., Reyes, A., Moore, A., Dantas, G., Gordon, J.I., 2011. Extensive personal human gut microbiota culture collections characterized and manipulated in gnotobiotic mice. Proc. Natl. Acad. Sci. https://doi.org/10.1073/pnas.1102938108.

Gordon, H.A., 1959. Morphological and physiological characterization of germfree life. Ann. N. Y. Acad. Sci. https://doi.org/10.1111/j.1749-6632.1959.tb53104.x.

Goyal, M.S., Venkatesh, S., Milbrandt, J., Gordon, J.I., Raichle, M.E., 2015. Feeding the brain and nurturing the mind: linking nutrition and the gut microbiota to brain development. Proc. Natl. Acad. Sci. https://doi.org/10.1073/pnas.1511465112.

Grice, E.A., Segre, J.A., 2011. The skin microbiome. Nat. Rev. Microbiol. https://doi.org/10.1038/nrmicro2537.

Handa, R.J., Burgess, L.H., Kerr, J.E., O'keefe, J.A., 1994. Gonadal steroid hormone receptors and sex differences in the hypothalamo-pituitary-adrenal axis. Horm. Behav. https://doi.org/10.1006/hbeh.1994.1044.

Handa, R.J., Weiser, M.J., 2014. Gonadal steroid hormones and the hypothalamo-pituitary-adrenal axis. Front. Neuroendocrinol. https://doi.org/10.1016/j.yfrne.2013.11.001.

Hantsoo, L., Jašarević, E., Criniti, S., McGeehan, B., Tanes, C., Sammel, M.D., Elovitz, M.A., Compher, C., Wu, G., Epperson, C.N., 2019. Childhood adversity impact on gut microbiota and inflammatory response to stress during pregnancy. Brain. Behav. Immun. 75, 240–250. https://doi.org/10.1016/j.bbi.2018.11.005.

Hart, M.L., Ericsson, A.L., Kent Loyd, K.C., Grimsmurd, K.N., Rogala, A.R., Godfrey, V.L., Nielsen, J.N., Franklin, C.L., 2018. Development of outbred CD1 mouse colonies with distinct standardized gut microbiota profiles for use in complex microbiota targeted studies. Sci Rep. https://doi.org/10.1038/s41598-018-28448-0.

Hay, P.E., Taylor-Robinson, D., Lamont, R.F., 1992. Diagnosis of bacterial vaginosis in a gynaecology clinic. BJOGAn Int. J. Obstet. Gynaecol. https://doi.org/10.1111/j.1471-0528.1992.tb14395.x.

Hill, D.A., Artis, D., 2010. Intestinal bacteria and the regulation of immune cell homeostasis. Annu. Rev. Immunol. https://doi.org/10.1146/annurev-immunol-030409-101330.

Hooper, L.V., Littman, D.R., Macpherson, A.J., 2012. Interactions between the microbiota and the immune system. Science (80-.). https://doi.org/10.1126/science.1223490.

Hyman, R.W., Fukushima, M., Jiang, H., Fung, E., Rand, L., Johnson, B., Vo, K.C., Caughey, A.B., Hilton, J.F., Davis, R.W., Giudice, L.C., 2014. Diversity of the vaginal microbiome correlates with preterm birth. Reprod. Sci. https://doi.org/10.1177/1933719113488838.

Ivanov, I.I., Atarashi, K., Manel, N., Brodie, E.L., Shima, T., Karaoz, U., Wei, D., Goldfarb, K.C., Santee, C.A., Lynch, S.V., Tanoue, T., Imaoka, A., Itoh, K., Takeda, K., Umesaki, Y., Honda, K., Littman, D.R., 2009. Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell. https://doi.org/10.1016/j.cell.2009.09.033.

Jašarević, E., Howard, C.D., Misic, A.M., Beiting, D.P., Bale, T.L., 2017. Stress during pregnancy alters temporal and spatial dynamics of the maternal and offspring microbiome in a sex-specific manner. Sci. Rep. https://doi.org/10.1038/srep44182.

Jašarević, E., Howard, C.D., Morrison, K., Misic, A., Weinkopff, T., Scott, P., Hunter, C., Beiting, D., Bale, T.L., 2018. The maternal vaginal microbiome partially mediates the effects of prenatal stress on offspring gut and hypothalamus. Nat. Neurosci. https://doi.org/10.1038/s41593-018-0182-5.

Jašarević, E., Howerton, C.L., Howard, C.D., Bale, T.L., 2015. Alterations in the vaginal microbiome by maternal stress are associated with metabolic reprogramming of the offspring gut and brain. Endocrinology. https://doi.org/10.1210/en.2015-1177.

Jašarević, E., Morrison, K.E., Bale, T.L., 2016. Sex differences in the gut microbiome – brain axis across the lifespan. Philos. Trans. R. Soc. B Biol. Sci. https://doi.org/10.1098/rstb.2015.0122.

Kabouridis, P.S., Pachnis, V., 2015. Emerging roles of gut microbiota and the immune system in the development of the enteric nervous system. J. Clin. Invest. https://doi.org/10.1172/JCI76308.

Kau, A.L., Ahern, P.P., Griffin, N.W., Goodman, A.L., Gordon, J.I., 2011. Human nutrition, the gut microbiome and the immune system. Nature. https://doi.org/10.1038/nature10213.

Kentner, A.C., Bilbo, S.D., Brown, A.S., Hsiao, E.Y., McAllister, A.K., Meyer, U., Pearce, B.D., Pletnikov, M.V., Yolken, R.H., Bauman, M.D., 2019. Maternal immune activation: reporting guidelines to improve the rigor, reproducibility, and transparency of the model. Neuropsychopharmacology. https://doi.org/10.1038/s41386-018-0185-7.

Kim, S., Kim, H., Yim, Y.S., Ha, S., Atarashi, K., Tan, T.G., Longman, R.S., Honda, K., Littman, D.R., Choi, G.B., Huh, J.R., 2017. Maternal gut bacteria promote neurodevelopmental abnormalities in mouse offspring. Nature. https://doi.org/10.1038/nature23910.

Klein, S.L., Flanagan, K.L., 2016. Sex differences in immune responses. Nat. Rev. Immunol. https://doi.org/10.1038/nri.2016.90.

Koren, O., Goodrich, J.K., Cullender, T.C., Spor, A., Laitinen, K., Kling Bäckhed, H., Gonzalez, A., Werner, J.J., Angenent, L.T., Knight, R., Bäckhed, F., Isolauri, E., Salminen, S., Ley, R.E., 2012. Host remodeling of the gut microbiome and metabolic changes during pregnancy. Cell. https://doi.org/10.1016/j.cell.2012.07.008.

Korpela, K., Costea, P., Coelho, L.P., Kandels-Lewis, S., Willemsen, G., Boomsma, D.I., Segata, N., Bork, P., 2018. Selective maternal seeding and environment shape the human gut microbiome. Genome Res. https://doi.org/10.1101/gr.233940.117.

Kuczynski, J., Lauber, C.L., Walters, W.A., Parfrey, L.W., Clemente, J.C., Gevers, D., Knight, R., 2012. Experimental and analytical tools for studying the human microbiome. Nat. Rev. Genet. https://doi.org/10.1038/nrg3129.

La Rosa, P.S., Warner, B.B., Zhou, Y., Weinstock, G.M., Sodergren, E., Hall-Moore, C.M., Stevens, H.J., Bennett, W.E., Shaikh, N., Linneman, L.A., Hoffmann, J.A., Hamvas, A., Deych, E., Shands, B.A., Shannon, W.D., Tarr, P.I., 2014. Patterned progression of bacterial populations in the premature infant gut. Proc. Natl. Acad. Sci. https://doi.org/10.1073/pnas.1409497111.

Lain, K.Y., Catalano, P.M., 2007. Metabolic changes in pregnancy. Clin. Obstet. Gynecol. https://doi.org/10.1097/GRF.0b013e31815a5494.

LeBlanc, J.G., Milani, C., de Giori, G.S., Sesma, F., van Sinderen, D., Ventura, M., 2013. Bacteria as vitamin suppliers to their host: a gut microbiota perspective. Curr. Opin. Biotechnol. https://doi.org/10.1016/j.copbio.2012.08.005.

Lecuit, M., Sonnenburg, J.L., Cossart, P., Gordon, J.I., 2007. Functional genomic studies of the intestinal response to a foodborne enteropathogen in a humanized gnotobiotic mouse model. J. Biol. Chem. https://doi.org/10.1074/jbc.M610926200.

Lee, A.H., Shannon, C.P., Amenyogbe, N., Bennike, T.B., Diray-Arce, J., Idoko, O.T., Gill, E.E., Ben-Othman, R., Pomat, W.S., van Haren, S.D., Cao, K.A.L., Cox, M., Darboe, A., Falsafi, R., Ferrari, D., Harbeson, D.J., He, D., Bing, C., Hinshaw, S.J., Ndure, J., Njie-Jobe, J., Pettengill, M.A., Richmond, P.C., Ford, R., Saleu, G., Masiria, G., Matlam, J.P., Kirarock, W., Roberts, E., Malek, M., Sanchez-Schmitz, G., Singh, A., Angelidou, A., Smolen, K.K., Brinkman, R.R., Ozonoff, A., Hancock, R.E.W., van den Biggelaar, A.H.J., Steen, H., Tebbutt, S.J., Kampmann, B., Levy, O., Kollmann, T.R., 2019. Dynamic molecular changes during the first week of human life follow a robust developmental trajectory. Nat. Commun. https://doi.org/10.1038/s41467-019-08794-x.

Levine, S., Sowinski, R., 1973. Experimental allergic encephalomyelitis in inbred and outbred mice. J. Immunol.

Li, X., Egervari, G., Wang, Y., Berger, S.L., Lu, Z., 2018. Regulation of chromatin and gene expression by metabolic enzymes and metabolites. Nat. Rev. Mol. Cell Biol. https://doi.org/10.1038/s41580-018-0029-7.

Littman, D.R., Pamer, E.G., 2011. Role of the commensal microbiota in normal and pathogenic host immune responses. Cell Host Microbe. https://doi.org/10.1016/j.chom.2011.10.004.

Lotz, M., Gutle, D., Walther, S., Menard, S., Bogdan, C., Hornef, M.W., 2006. Postnatal acquisition of endotoxin tolerance in intestinal epithelial cells. J. Exp. Med. https://doi.org/10.1084/jem.20050625.

Ma, B., Forney, L.J., Ravel, J., 2012. Vaginal microbiome: rethinking health and disease. Annu. Rev. Microbiol. https://doi.org/10.1146/annurev-micro-092611-150157.

Ma, J., Prince, A.L., Bader, D., Hu, M., Ganu, R., Baquero, K., Blundell, P., Alan Harris, R., Frias, A.E., Grove, K.L., Aagaard, K.M., 2014. High-fat maternal diet during pregnancy persistently alters the offspring microbiome in a primate model. Nat. Commun.

https://doi.org/10.1038/ncomms4889.
Mackie, R.I., Sghir, A., Gaskins, H.R., 1999. Developmental microbial ecology of the neonatal gastrointestinal tract. Am. J. Clin. Nutr.
Markle, J.G., Frank, D.N., Adeli, K., Von Bergen, M., Danska, J.S., 2014. Microbiome manipulation modifies sex-specific risk for autoimmunity. Gut Microbes. https://doi.org/10.4161/gmic.29795.
Markle, J.G.M., Frank, D.N., Mortin-Toth, S., Robertson, C.E., Feazel, L.M., Rolle-Kampczyk, U., Von Bergen, M., McCoy, K.D., Macpherson, A.J., Danska, J.S., 2013. Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. Science (80-.). https://doi.org/10.1126/science.1233521.
Masten, A.S., Best, K.M., Garmezy, N., 1990. Resilience and development: contributions from the study of children who overcome adversity. Dev. Psychopathol. https://doi.org/10.1017/S0954579400005812.
Matcovitch-Natan, O., Winter, D.R., Giladi, A., Aguilar, S.V., Spinrad, A., Sarrazin, S., Ben-Yehuda, H., David, E., González, F.Z., Perrin, P., Keren-Shaul, H., Gury, M., Lara-Astaiso, D., Thaiss, C.A., Cohen, M., Halpern, K.B., Baruch, K., Deczkowska, A., Lorenzo-Vivas, E., Itzkovitz, S., Elinav, E., Sieweke, M.H., Schwartz, M., Amit, I., 2016. Microglia development follows a stepwise program to regulate brain homeostasis. Science 353, aad8670. https://doi.org/10.1126/science.aad8670.
Metchnikoff, O., 1921. Life of Elie Metchnikoff 1845–1916. Houghton Mifflin Company.
Mirpuri, J., Raetz, M., Sturge, C.R., Wilhelm, C.L., Benson, A., Savani, R.C., Hooper, L.V., Yarovinsky, F., 2013. Proteobacteria-specific IgA regulates maturation of the intestinal microbiota. Gut Microbes. https://doi.org/10.4161/gmic.26489.
Morgan, C.P., Chan, J.C., Bale, T.L., 2019. Driving the next generation: paternal lifetime experiences transmitted via extracellular vesicles and their small RNA cargo. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2018.09.007.
Mueller, N.T., Bakacs, E., Combellick, J., Grigoryan, Z., Dominguez-Bello, M.G., 2015. The infant microbiome development: mom matters. Trends Mol. Med. https://doi.org/10.1016/j.molmed.2014.12.002.
Neuman, H., Debelius, J.W., Knight, R., Koren, O., 2015. Microbial endocrinology: the interplay between the microbiota and the endocrine system. FEMS Microbiol. Rev. https://doi.org/10.1093/femsre/fuu010.
Neuman, H., Koren, O., 2017. The Pregnancy Microbiome. In: Nestle Nutrition Institute Workshop Series. https://doi.org/10.1159/000455207.
Nobel, Y.R., Cox, L.M., Kirigin, F.F., Bokulich, N.A., Yamanishi, S., Teitler, I., Chung, J., Sohn, J., Barber, C.M., Goldfarb, D.S., Raju, K., Abubucker, S., Zhou, Y., Ruiz, V.E., Li, H., Mitreva, M., Alekseyenko, A.V., Weinstock, G.M., Sodergren, E., Blaser, M.J., 2015. Metabolic and metagenomic outcomes from early-life pulsed antibiotic treatment. Nat. Commun. https://doi.org/10.1038/ncomms8486.
Nugent, B.M., Bale, T.L., 2015. The omniscient placenta: metabolic and epigenetic regulation of fetal programming. Front. Neuroendocrinol. https://doi.org/10.1016/j.yfrne.2015.09.001.
Nuriel-Ohayon, M., Neuman, H., Koren, O., 2016. Microbial changes during pregnancy, birth, and infancy. Front. Microbiol. https://doi.org/10.3389/fmicb.2016.01031.
O'Malley, K., Crooks, J., Duke, E., Stevenson, I.H., 1971. Effect of age and sex on human drug metabolism. Br. Med. J. https://doi.org/10.1136/bmj.3.5775.607.
Nuriel-Ohayon, M., Neuman, H., Ziv, O., Belogolovski, A., Barsheshet, Y., Bloch, N., Uzan, A., Lahav, R., Peretz, A., Frishman, S., Hod, M., Hadar, E., Louzoun, Y., Avni, O., Koren, O., 2019. Progesterone Increases Bifidobacterium Relative Abundance during Late Pregnancy. Cell Rep. 27, 730–736.e3. https://doi.org/10.1016/j.celrep.2019.03.075.
Ober, C., Loisel, D.A., Gilad, Y., 2008. Sex-specific genetic architecture of human disease. Nat. Rev. Genet. https://doi.org/10.1038/nrg2415.
Olin, A., Henckel, E., Chen, Y., Lakshmikanth, T., Pou, C., Mikes, J., Gustafsson, A., Bernhardsson, A.K., Zhang, C., Bohlin, K., Brodin, P., 2018. Stereotypic immune system development in newborn children. Cell. https://doi.org/10.1016/j.cell.2018.06.045.
Pasolli, E., Asnicar, F., Manara, S., Zolfo, M., Karcher, N., Armanini, F., Beghini, F., Manghi, P., Tett, A., Ghensi, P., Collado, M.C., Rice, B.L., DuLong, C., Morgan, X.C., Golden, C.D., Quince, C., Huttenhower, C., Segata, N., 2019. Extensive unexplored human microbiome diversity revealed by over 150,000 genomes from metagenomes spanning age, geography, and lifestyle. Cell. https://doi.org/10.1016/j.cell.2019.01.001.
Prince, A.L., Antony, K.M., Ma, J., Aagaard, K.M., 2014. The microbiome and development: a mother's perspective. Semin. Reprod. Med. https://doi.org/10.1055/s-0033-1361818.
Pronovost, G.N., Hsiao, E.Y., 2019. Perinatal interactions between the microbiome, immunity, and neurodevelopment. Immunity. https://doi.org/10.1016/j.immuni.2018.11.016.
Qin, J., Li, R., Raes, J., et al., 2010. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. https://doi.org/10.1038/nature08821.
Ravel, J., Gajer, P., Abdo, Z., Schneider, G.M., Koenig, S.S.K., McCulle, S.L., Karlebach, S., Gorle, R., Russell, J., Tacket, C.O., Brotman, R.M., Davis, C.C., Ault, K., Peralta, L., Forney, L.J., 2011. Vaginal microbiome of reproductive-age women. Proc. Natl. Acad. Sci. https://doi.org/10.1073/pnas.1002611107.
Ricci, M., 2013. The importance of a proper control diet. Res. Diets Focus.
Ridaura, V.K., Faith, J.J., Rey, F.E., Cheng, J., Duncan, A.E., Kau, A.L., Griffin, N.W., Lombard, V., Henrissat, B., Bain, J.R., Muehlbauer, M.J., Ilkayeva, O., Semenkovich, C.F., Funai, K., Hayashi, D.K., Lyle, B.J., Martini, M.C., Ursell, L.K., Clemente, J.C., Van Treuren, W., Walters, W.A., Knight, R., Newgard, C.B., Heath, A.C., Gordon, J.I., 2013. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science (80-). https://doi.org/10.1126/science.1241214.
Romero, R., Hassan, S.S., Gajer, P., Tarca, A.L., Fadrosh, D.W., Bieda, J., Chaemsaithong, P., Miranda, J., Chaiworapongsa, T., Ravel, J., 2014a. The vaginal microbiota of pregnant women who subsequently have spontaneous preterm labor and delivery and those with a normal delivery at term. Microbiome. https://doi.org/10.1186/2049-2618-2-18.
Romero, R., Hassan, S.S., Gajer, P., Tarca, A.L., Fadrosh, D.W., Nikita, L., Galuppi, M., Lamont, R.F., Chaemsaithong, P., Miranda, J., Chaiworapongsa, T., Ravel, J., 2014b. The composition and stability of the vaginal microbiota of normal pregnant women is different from that of non-pregnant women. Microbiome. https://doi.org/10.1186/2049-2618-2-4.
Rosshart, S.P., Herz, J., Vassallo, B.G., Hunter, A., Wall, M.K., Badger, J.H., McCulloch, J.A., Anastasakis, D.G., Sarshad, A.A., Leonardi, I., Collins, N., Blatter, J.A., Han, S.-I., Tamoutounour, S., Potapova, S., St, Foster, Claire, M.B., Yuan, W., Sen, S.K., Dreier, M.S., Hild, B., Hafner, M., Wang, D., Iliev, I.D., Belkaid, Y., Trinchieri, G., Rehermann, B., 2019. Laboratory mice born to wild mice have natural microbiota and model human immune response. Science. https://doi.org/10.1126/science.aaw4361.
Round, J.L., Mazmanian, S.K., 2009. The gut microbiota shapes intestinal immune responses during health and disease. Nat. Rev. Immunol. https://doi.org/10.1038/nri2515.
Sampson, T.R., Mazmanian, S.K., 2015. Control of brain development, function, and behavior by the microbiome. Cell Host Microbe. https://doi.org/10.1016/j.chom.2015.04.011.
Samuel, B.S., Gordon, J.I., 2006. A humanized gnotobiotic mouse model of host-archaeal-bacterial mutualism. Proc. Natl. Acad. Sci. https://doi.org/10.1073/pnas.0602187103.
Sarkar, A., Harty, S., Lehto, S.M., Moeller, A.H., Dinan, T.G., Dunbar, R.I.M., Cryan, J.F., Burnet, P.W.J., 2018. The microbiome in psychology and cognitive neuroscience. Trends Cogn. Sci. https://doi.org/10.1016/j.tics.2018.04.006.
Schmidt, T.S.B., Raes, J., Bork, P., 2018. The human gut microbiome: from association to modulation. Cell. https://doi.org/10.1016/j.cell.2018.02.044.
Schwiertz, A., Gruhl, B., Löbnitz, M., Michel, P., Radke, M., Blaut, M., 2003. Development of the intestinal bacterial composition in hospitalized preterm infants in comparison with breast-fed, full-term infants. Pediatr. Res. https://doi.org/10.1203/01.PDR.0000078274.74607.7A.
Sherwin, E., Dinan, T.G., Cryan, J.F., 2018. Recent developments in understanding the role of the gut microbiota in brain health and disease. Ann. N. Y. Acad. Sci. https://doi.org/10.1111/nyas.13416.
Smith, M.I., Yatsunenko, T., Manary, M.J., Trehan, I., Mkakosya, R., Cheng, J., Kau, A.L., Rich, S.S., Concannon, P., Mychaleckyj, J.C., Liu, J., Houpt, E., Li, J. V., Holmes, E., Nicholson, J., Knights, D., Ursell, L.K., Knight, R., Gordon, J.I., 2013. Gut microbiomes of Malawian twin pairs discordant for kwashiorkor. Science (80-.). https://doi.org/10.1126/science.1229000.
Smith, S.E.P., Li, J., Garbett, K., Mirnics, K., Patterson, P.H., 2007. Maternal immune activation alters fetal brain development through interleukin-6. J. Neurosci. https://doi.org/10.1523/JNEUROSCI.2178-07.2007.
Sonnenburg, E.D., Smits, S.A., Tikhonov, M., Higginbottom, S.K., Wingreen, N.S., Sonnenburg, J.L., 2016. Diet-induced extinctions in the gut microbiota compound over generations. Nature. https://doi.org/10.1038/nature16504.
Stappenbeck, T.S., Virgin, H.W., 2016. Accounting for reciprocal host-microbiome interactions in experimental science. Nature. https://doi.org/10.1038/nature18285.
Stearns, J.C., Simioni, J., Gunn, E., McDonald, H., Holloway, A.C., Thabane, L., Mousseau, A., Schertzer, J.D., Ratcliffe, E.M., Rossi, L., Surette, M.G., Morrison, K.M., Hutton, E.K., 2017. Intrapartum antibiotics for GBS prophylaxis alter colonization patterns in the early infant gut microbiome of low risk infants. Sci. Rep. https://doi.org/10.1038/s41598-017-16606-9.
Steliou, K., Boosalis, M.S., Perrine, S.P., Sangerman, J., Faller, D.V., 2012. Butyrate histone deacetylase inhibitors. Biores. Open Access. https://doi.org/10.1089/biores.2012.0223.
Stewart, C.J., Ajami, N.J., O'Brien, J.L., Hutchinson, D.S., Smith, D.P., Wong, M.C., Ross, M.C., Lloyd, R.E., Doddapaneni, H.V., Metcalf, G.A., Muzny, D., Gibbs, R.A., Vatanen, T., Huttenhower, C., Xavier, R.J., Rewers, M., Hagopian, W., Toppari, J., Ziegler, A.G., She, J.X., Akolkar, B., Lernmark, A., Hyoty, H., Vehik, K., Krischer, J.P., Petrosino, J.F., 2018. Temporal development of the gut microbiome in early childhood from the TEDDY study. Nature. https://doi.org/10.1038/s41586-018-0617-x.
Subramanian, S., Blanton, L.V., Frese, S.A., Charbonneau, M., Mills, D.A., Gordon, J.I., 2015. Cultivating healthy growth and nutrition through the gut microbiota. Cell. https://doi.org/10.1016/j.cell.2015.03.013.
Subramanian, S., Huq, S., Yatsunenko, T., Haque, R., Mahfuz, M., Alam, M.A., Benezra, A., Destefano, J., Meier, M.F., Muegge, B.D., Barratt, M.J., VanArendonk, L.G., Zhang, Q., Province, M.A., Petri, W.A., Ahmed, T., Gordon, J.I., 2014. Persistent gut microbiota immaturity in malnourished Bangladeshi children. Nature. https://doi.org/10.1038/nature13421.
Sudo, N., Chida, Y., Aiba, Y., Sonoda, J., Oyama, N., Yu, X.-N., Kubo, C., Koga, Y., 2004. Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice. J. Physiol. 558, 263–275. https://doi.org/10.1113/jphysiol.2004.063388.
Thion, M.S., Ginhoux, F., Garel, S., 2018. Microglia and early brain development: an intimate journey. Science (80-.). https://doi.org/10.1126/science.aat0474.
Turnbaugh, P.J., Bäckhed, F., Fulton, L., Gordon, J.I., 2008. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host Microbe. https://doi.org/10.1016/j.chom.2008.02.015.
Turnbaugh, P.J., Hamady, M., Yatsunenko, T., Cantarel, B.L., Duncan, A., Ley, R.E., Sogin, M.L., Jones, W.J., Roe, B.A., Affourtit, J.P., Egholm, M., Henrissat, B., Heath, A.C., Knight, R., Gordon, J.I., 2009a. A core gut microbiome in obese and lean twins. Nature. https://doi.org/10.1038/nature07540.
Turnbaugh, P.J., Ley, R.E., Mahowald, M.A., Magrini, V., Mardis, E.R., Gordon, J.I., 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. https://doi.org/10.1038/nature05414.
Turnbaugh, P.J., Ridaura, V.K., Faith, J.J., Rey, F.E., Knight, R., Gordon, J.I., 2009b. The

effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. Sci. Transl. Med. https://doi.org/10.1126/scitranslmed.3000322.

Vrbanac, A., Riestra, A.M., Coady, A., Knight, R., Nizet, V., Patras, K.A., 2018. The murine vaginal microbiota and its perturbation by the human pathogen group B Streptococcus. BMC Microbiol. 18, 197. https://doi.org/10.1186/s12866-018-1341-2.

Vuong, H.E., Yano, J.M., Fung, T.C., Hsiao, E.Y., 2017. The microbiome and host behavior. Annu. Rev. Neurosci. https://doi.org/10.1146/annurev-neuro-072116-031347.

Wampach, L., Heintz-Buschart, A., Fritz, J.V., Ramiro-Garcia, J., Habier, J., Herold, M., Narayanasamy, S., Kaysen, A., Hogan, A.H., Bindl, L., Bottu, J., Halder, R., Sjöqvist, C., May, P., Andersson, A.F., de Beaufort, C., Wilmes, P., 2018. Birth mode is associated with earliest strain-conferred gut microbiome functions and immunostimulatory potential. Nat. Commun. https://doi.org/10.1038/s41467-018-07631-x.

Warden, C.H., Fisler, J.S., 2008. Comparisons of diets used in animal models of high-fat feeding. Cell Metab. https://doi.org/10.1016/j.cmet.2008.03.014.

Warner, B.B., 2019. The contribution of the gut microbiome to neurodevelopment and neuropsychiatric disorders. Pediatr. Res. https://doi.org/10.1038/s41390-018-0191-9.

Watanabe, H., Numata, K., Ito, T., Takagi, K., Matsukawa, A., 2004. Innate immune response in Th1- and Th2-dominant mouse strains. Shock. https://doi.org/10.1097/01.shk.0000142249.08135.e9.

Yassour, M., Jason, E., Hogstrom, L.J., Arthur, T.D., Tripathi, S., Siljander, H., Selvenius, J., Oikarinen, S., Hyöty, H., Virtanen, S.M., Ilonen, J., Ferretti, P., Pasolli, E., Tett, A., Asnicar, F., Segata, N., Vlamakis, H., Lander, E.S., Huttenhower, C., Knip, M., Xavier, R.J., 2018. Strain-level analysis of mother-to-child bacterial transmission during the first few months of life. Cell Host Microbe. https://doi.org/10.1016/j.chom.2018.06.007.

Yatsunenko, T., Rey, F.E., Manary, M.J., Trehan, I., Dominguez-Bello, M.G., Contreras, M., Magris, M., Hidalgo, G., Baldassano, R.N., Anokhin, A.P., Heath, A.C., Warner, B., Reeder, J., Kuczynski, J., Caporaso, J.G., Lozupone, C.A., Lauber, C., Clemente, J.C., Knights, D., Knight, R., Gordon, J.I., 2012. Human gut microbiome viewed across age and geography. Nature. https://doi.org/10.1038/nature11053.

Yurkovetskiy, L., Burrows, M., Khan, A.A., Graham, L., Volchkov, P., Becker, L., Antonopoulos, D., Umesaki, Y., Chervonsky, A.V., 2013. Gender bias in autoimmunity is influenced by microbiota. Immunity. https://doi.org/10.1016/j.immuni.2013.08.013.

Zhou, X., Brown, C.J., Abdo, Z., Davis, C.C., Hansmann, M.A., Joyce, P., Foster, J.A., Forney, L.J., 2007. Differences in the composition of vaginal microbial communities found in healthy Caucasian and black women. ISME J. https://doi.org/10.1038/ismej.2007.12.

Zijlmans, M.A.C., Korpela, K., Riksen-Walraven, J.M., de Vos, W.M., de Weerth, C., 2015. Maternal prenatal stress is associated with the infant intestinal microbiota. Psychoneuroendocrinology. https://doi.org/10.1016/j.psyneuen.2015.01.006.

Zou, J., Chassaing, B., Singh, V., Pellizzon, M., Ricci, M., Fythe, M.D., Kumar, M.V., Gewirtz, A.T., 2018. Fiber-mediated nourishment of gut microbiota protects against diet-induced obesity by restoring IL-22-mediated colonic health. Cell Host Microbe. https://doi.org/10.1016/j.chom.2017.11.003.