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The Maternal Microbiome: cause or consequence of obesity risk in the next generation?

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The transfer of bacteria from the pregnant mother to the fetus is universal in the animal kingdom. Exposure of the fetal intestine to microbes, possibly even through amniotic fluid, is an important contributor to gut maturation and by extension to infant health. Animal and human data strongly suggest that the composition of the neonatal gut microbiota is dependent both on maternal obesity and maternal diet during pregnancy and lactation (1,2), and on mode of delivery (2). The microbiome plays a major role in nutrition, metabolism, protection against pathogens, resistance to infections, and immune system development. However, looking for a link between microbial transfer from mother to infant and disease pathways requires characterizing what is normal, which is not so easy. One thing that is becoming clear, however, is that the developing infant gut microbiome, whether due to metabolism or cross-talk with the infant immune system, may hold the key to understanding the early origins of multiple disease pathways.

The causal role of the gut microbiota on obesity through microbial transfer experiments from humans to germ-free (GF) mice (3) and from healthy human donors to subjects with obesity (4), demonstrates that microbiota from a healthy donor can improve the body weight of a recipient with obesity, albeit in the short-term. GF mice provide exciting and compelling mechanistic data, with caution due to the immature immune system and relative differences

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in microbial taxa between humans and mice. Recent evidence from our laboratory (5) and others (2) showed that infants of overweight mothers and mothers with obesity have an altered bacterial composition compared with vaginally-delivered infants born to normal-weight mothers, as early as 2 days of life. Proteobacteria, an early pioneering bacteria important for education of the newborn immune system(s), was depleted in infants from mothers with obesity delivered vaginally but not in infants from mothers with obesity delivered by cesarean section (2). Proteobacteria were also lower in stool samples from 2-week-old infants born to normal-weight women who had excess (>20 kg) gestational weight gain (JE Friedman, unpublished results).

Whether reduced Proteobacteria abundance is due to maternal diet, changes in breast milk composition, or other factors is not entirely clear. Human milk oligosaccharides also exert a powerful impact on the colonization and temporal development of the infant gut microbiota. This field of research is rapidly emerging and includes deeper phenotypic characterization of bioactive components of human milk. In non-human primates, feeding a high-fat diet during pregnancy and lactation (whether mothers were obese or not) resulted in depleted Proteobacteria and enriched Firmicutes in juvenile (1-year-old) offspring, despite weaning to a normal low-fat chow diet (1). The observation that maternal diet establishes long-lasting effects on gut microbial composition in the offspring has profound clinical implications, and emphasizes the need to target maternal diet during pregnancy and lactation rather than focusing on maternal weight in the prevention of a less diverse infant microbiota during the critical first year of life. Evidence also suggests cesarean birth or lack of breastfeeding results in a higher obesity risk, even in offspring of normal-weight mothers, perhaps due to differences in gastrointestinal microbiota.

The immune system is the first line of adaptation to changes in the microbiome. Due to the abundance of oxygen in the neonatal gut, the microbiota in the first weeks of life is frequently dominated by the aerobic Proteobacteria species (e.g., *Escherichia*, *Klebsiella*, and *Enterobacter*). These facultative aerobes make the habitat suitable for colonization by strict anaerobes, by consuming oxygen, altering the pH, lowering the redox potential, and producing carbon dioxide and nutrients. In adults, Proteobacteria, potent LPS producers, are associated with inflammation and are elevated in conditions like obesity. However, in infants, the presence of this early colonizer is an important component in the establishment of gut-host homeostasis, specifically activation of the adaptive immune system and development of the innate immune system to commensal microbes. In mice, early exposure to Proteobacteria is essential for driving the early inflammatory changes necessary for protection against excessive inflammatory and autoimmune gastrointestinal disorders later in life (6); this is sometimes referred to as a “priming” or “trained immunity” effect (7). The effects of a relative depletion of intestinal Proteobacteria species in neonates of mothers with obesity could cause persistent alterations in immune development and increase an infant's risk of developing inflammatory and metabolic diseases (see Figure 1), but the literature on this topic is scarce.

Because immune development in the infant is highly dependent on triggers provided by the mother's microbiota (8), altered gut microbes in infants of mothers with obesity could cause developmental programming to a proinflammatory phenotype. Alterations in the intestinal

environment are directly involved in mucosal inflammation and disease, autoimmunity, and allergic disorders in childhood and adulthood (9). Dysbiosis of the gut microbiota has been correlated with nonalcoholic fatty liver disease (NAFLD) in children and adults; however, how the early life microbial composition influences hepatic fat accumulation and inflammation before the disease occurs is unclear. Intriguingly, maternal obesity in mice was recently shown to alter social brain programming by altering gut microbiota in progeny (10). Social deficits, including the dopamine reward system, and gut microbiota dysbiosis in offspring from high-fat diet-fed mothers was transferable to GF mice, suggesting the potential for discovery of specific microbes with new functions that impact brain health, including neurotransmitters that affect satiety.

In summary, the causative role of bacteria and early inflammation in the infant is not well studied. An altered gut microbial composition in infants born to mothers with obesity or on a high-fat diet could cause developmental programming to a proinflammatory phenotype. Cesarean delivery, or lack of breastfeeding, which is more likely in mothers with obesity, may also contribute to atopic diseases or obesity risks later in life. Given that early infant weight gain and inflammatory changes in early life can have lifelong consequences for metabolic health, ongoing studies may provide clues to the effects of maternal obesity and/or diet to prime the infant gut microbiota, with possible functional effects of specific bacterial strains on metabolic and immunologic health.

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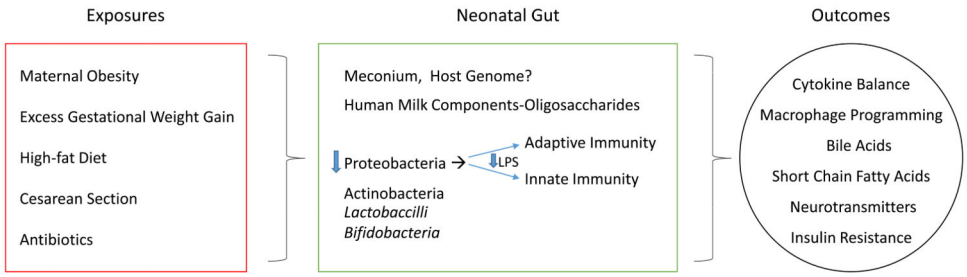

Figure 1.

Maternal-fetal exposures and how early microbial shifts may influence the development of infant immunity with potential outcomes on childhood metabolism and energy balance. LPS, lipopolysaccharide