MILESTONE 4

The microbiota influences metabolism of host-directed drugs

Peppercorn and Goldman demonstrated that the anti-inflammatory drug, salicylazosulfapyridine, could be degraded in conventional rats and when cultured with human gut bacteria, but not in germ-free rats, indicating a role for the gut microbiota in drug transformations. An increasing number of studies have confirmed the role of the microbiota, not limited to the gut, in drug metabolism and highlighted the implications for drug inactivation, efficacy and toxicity.

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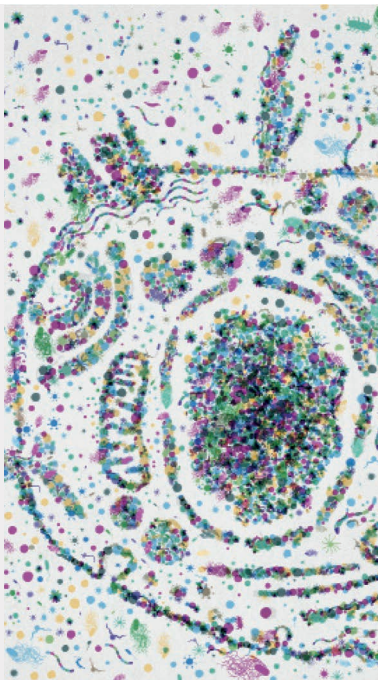

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MILESTONE 5

Microbiota succession in early life

Early life experiences have complex and long-lasting effects that can reach into adulthood — the same can be said of the acquisition and succession of our microbiota during the first years of life. The culmination of years of investigation from many laboratories has led to an in-depth characterization of postnatal microbial acquisition and maturation during the first years of life, and has led to the realisation that this represents a crucial window in our long-term development.

Early studies, dating as far back as 1900, described various aspects of bacterial succession in infants, but in 1981, three studies were reported that set out to quantitatively characterize early acquisition of gut commensals and to study how feeding shapes our initial microbiota. In one study, development of the bacterial community was investigated in infants in Sheffield, England, by culturing specimens taken from the meconium (a baby's first faeces), faeces, mouth and umbilicus in the first six days of life. In another study, the faecal bacterial community was compared between infant cohorts in France that were either bottle-fed or breastfed; and in the third study, faecal bacterial communities from breastfed infants, weaned children and adults born in urban England and rural Nigeria, were compared. These studies provided quantitative measurements of specific bacterial taxa in early life, giving insight into the pioneer species that colonize the infant gut. This paved the way for future high-resolution studies of microbial succession in infants.

With the advent of 'omics' technologies in the following decades, our understanding of when the majority of our microbiota are acquired, and of what species are there, has heightened and the importance of host–microbiota–environment interactions during early life has become realised. The infant gut microbiota undergoes a period of massive change in the first years of life. The initial microbiota adapts over time and is shaped by the availability of different nutrients. As the infant consumes increasingly more complex dietary substrates, there are shifts in composition and an enrichment of bacterial functions related to carbohydrate metabolism and the biosynthesis of amino acids and vitamins. By 2–3 years of age, a stable microbiota develops that resembles that of the adults in the infant's community (see MILESTONE 7).

> "The infant gut microbiota undergoes a period of massive change in the first years of life"

When colonization first occurs is an open question; however, most scientists think that the foetus develops in a sterile environment and that we acquire the bulk of our initial microbiota during and immediately after birth. Recently, a few studies have found traces of bacterial DNA in the placenta, in the amniotic fluid that surrounds the foetus and in the meconium — suggesting prenatal colonization. However, many scientists think these findings could be the result of contamination and the debate is ongoing. Regardless of possible exposure to microorganisms in utero, the foetus is exposed to microbial molecules that cross the placenta from the mother.

The first major exposure to microorganisms happens during delivery, and is highly dependent on the mode of delivery. The microbiota of neonates that are born vaginally are enriched in bacteria that resemble

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the maternal vaginal microbiota (for example, *Lactobacillus* species), whereas neonates delivered by caesarean (C-) section lack these species and are instead enriched in skin commensals such as *Staphylococcus*, *Streptococcus* and *Propionibacterium* species. Over time, these differences gradually reduce between vaginally and C-section-born infants; however, in one study, bacteria associated with C-section remained associated with C-section-delivered infants up to two years of age, showing that birth mode could have long-term impacts on the microbiota.

Postnatal factors further configure the microbiota in early life. Breastmilk contains a complex community of bacteria that may help seed the infant gut microbiota, and in breastfed infants the gut microbiota is dominated by species that metabolise human milk oligosaccharides. Overall, diet has been found to be a major determinant of the infant gut microbiota. Studies of malnourished infants have shown that maturation of the gut microbiota does not occur in a similar manner to healthy infants, even after dietary intervention, and it has been proposed that an 'undernourished' microbiome in infancy can perpetuate growth impairments later in life.

The environment and people that surround an infant are also a source of microorganisms that can colonize various body sites. Genetically unrelated parents and even pets share a high proportion of their microbiota with infants. Genetics also has a role in determining our microbiota make-up, as evidenced by associations between the heritability of specific taxa and host genes.

The use of antimicrobials, which is essential for preserving life when infants acquire a serious bacterial infection, can impact the ecological succession of the infant microbiota. Antibiotics can impair the diversity and stability of the developing microbiota in infants, with abundances of specific taxa remaining reduced for years after treatment. The impact of antibiotics on the infant microbiota could have long-lasting health implications and their use in early life has been linked to an increased risk of several diseases, including asthma, inflammatory bowel disease and allergies (see MILESTONE 9). More research is required to uncover the underlying mechanisms; however, what is clear is that the microbiota has a vital role in immune, endocrine, metabolic and a variety of other developmental pathways in infants, and without it we would not be here today.

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Nature Reviews Microbiology

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