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# The link between obesity and the gut microbiota and immune system in early-life

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## ABSTRACT

In early-life, the gut microbiota is highly modifiable, being modulated by external factors such as maternal microbiota, mode of delivery, and feeding strategies. The composition of the child's gut microbiota will deeply impact the development and maturation of its immune system, with consequences for future health. As one of the main sources of microorganisms to the child, the mother represents a crucial factor in the establishment of early-life microbiota, impacting the infant's wellbeing. Recent studies have proposed that dysbiotic maternal gut microbiota could be transmitted to the offspring, influencing the development of its immunity, and leading to the development of diseases such as obesity. This paper aims to review recent findings in gut microbiota and immune system interaction in early-life, highlighting the benefits of a balanced gut microbiota in the regulation of the immune system.

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## 1. Gut microbiota and early-life development

Humans are heavily colonized by different microbial communities, which constitute the human microbiota. These collections of microorganisms can be encountered in different locations of the human body, as skin, nasal cavity, urogenital tract, oral cavity, and gut, where microbial density and diversity are higher (Amabebe *et al.* 2020). The gut microbiota is composed of commensal bacteria, fungi, viruses, and protozoa, which establish a symbiotic relationship with the host, as well as opportunistic microorganisms that may become pathogenic if a disruption in the intestinal microbial community occurs (Milani *et al.* 2017). The intestinal microbiome is dynamic, suffering alterations due to several host-related factors, such as age, health status, diet, antibiotics intake, and probiotics/prebiotics consumption (Singh *et al.* 2021).

The gut microbiota exerts a crucial role in the maintenance of homeostasis and the overall body balance, being involved in numerous physiological processes, such as 1) breakdown of unabsorbed

carbohydrates from digestion; 2) synthesis of beneficial microbial metabolites and vitamins as short-chain fatty acids (SCFA) and vitamin K; 3) mood regulation through the gut-brain-axis, by the production of tryptophan, a serotonin precursor, and other mechanisms; 4) protection against external pathogens by the competition with adhesion sites and/or release of antimicrobials; and 5) immunoregulation, meaning modulation of the immune response to internal or external stimuli (Singh *et al.* 2021; Ruan *et al.* 2020). In fact, the stimulation and regulation of the immune system are two of the most important functions executed by the gut microbiota. The gut microbiota and the immune system are closely related, and any disturbance to the delicate balance of intestinal microbial communities may lead to the development of diseases such as allergies, metabolic and gastrointestinal (GI) disorders like inflammatory bowel disease (Singh *et al.* 2021). This intimate link between gut microbes and immunity begins early in life, with the initial colonization of the GI tract of the infant. It was stated that the colonization of the GI tract starts at

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birth, during the passage through the birth canal, and further continues after birth according to the “sterile womb” theory (Escherich 1988; de Goffau *et al.* 2019). However, this topic remains controversial, since some studies have detected microbial particles, through 16S rRNA sequencing, in the umbilical cord blood, placenta, and meconium from healthy pregnancies (without reporting any infections), suggesting that microbial acquisition rather begins in the utero (Senn *et al.* 2020; Payne and Bayatibojakhi 2014; Aagaard *et al.* 2014; Rautava *et al.* 2012). Nevertheless, both theories (the “sterile womb” theory and the theory that suggests *in-utero* colonization) highlight the important role the maternal microbiome plays as the main source of microorganisms for the offspring in early-life, influencing the initial microbial colonization patterns, through the vertical transmission of microbiota.

At birth, the gut of the infant is rapidly colonized by a wide array of microbes, mainly by facultative anaerobes, such as *Staphylococcus* spp., *Streptococcus* spp., *Enterobacter* spp., and other members of the *Enterobacteriaceae* family (Lin *et al.* 2022; Martin *et al.* 2016). Although these microorganisms may perform aerobic and anaerobic respiration as well fermentation, normally they prefer aerobic respiration when oxygen is available due to its high energetic gain. Therefore, their presence leads to a gradual depletion of the intestinal oxygen and reducing intestinal oxidation-reduction potential within 48 h of birth, which facilitates the colonization of strict anaerobic bacteria such as *Bifidobacterium*, *Clostridia*, and *Bacteroides* (Lin *et al.* 2022). Moreover, it is believed that microbial colonization patterns are heavily influenced by the mode of delivery. For instance, vaginally delivered infants will be exposed to the vaginal and intestinal microbiota of the mother, essentially composed of *Lactobacillus* and *Prevotella*. Infants born through this route normally exhibit a more diverse gut microbiota (Milani *et al.* 2017; Martin *et al.* 2016). Concerning children born by cesarean, the microorganisms from the skin of the mother and hospital environment promote the initial exposure, presenting different colonization patterns in comparison to vaginally delivered infants. In this case, the gut microbiota of the infant will be colonized by *Staphylococcus* and *Clostridium*, and it is characterized by low microbial diversity and richness (Milani *et al.* 2017; Martin *et al.* 2016). Furthermore, cesarean-delivered infants experienced a delay in colonization by *Bifidobacterium* (Isolauri 2012).

Due to its plastic and dynamic characteristics, early-life microbiota can be altered or modulated by external factors, namely early-life diet (breastfeeding or formula) (Chichlowski *et al.* 2023; Pärnänen *et al.* 2022),

gestational age at birth (Sim *et al.* 2023), and maternal health or habits (Jones *et al.* 2024; Ren *et al.* 2023).

Early-life gut microbiota can differ between term and preterm infants. Compared to term infants, preterm newborns exhibit lower microbial diversity, and experience a delay in the establishment of a healthy microbiota, due to the overgrowth of certain bacterial species, such as *Enterococcus* (commonly associated with nosocomial infections, and consistent with a hospital stay) (Korpela *et al.* 2018; Rougé *et al.* 2010). It is also known that preterm babies are at higher risk of developing complications, often requiring invasive medical interventions, antibiotic administration, and a stay at the Neonatal Intensive Care Unit (NICU) (Henderickx *et al.* 2019). A study by Chi *et al.* (2019) found that the gut microbiota of preterm infants was enriched in *Klebsiella*, a microorganism often implicated in hospital infections, that may be transmitted through medical procedures [22]. Following the line of reasoning that implicates early-life clinical care and hospitalization in preterm intestinal microbiota changes, Yap and colleagues evaluated the impact of neonatal care practices and NICU admission in the microbiota of preterm and term infants, from day one (after birth) to 12 months postpartum. The authors observed significant differences between term and preterm infants, in  $\beta$ -diversity, revealing a clear separation between the two groups, particularly at 6 and 12 months. In terms of taxa, Bacillota (former Firmicutes) and Bacteroidota (former Bacteroidetes) were the taxa that distinguish between term and preterm infants. Furthermore, in the first two weeks of life, the levels of *Klebsiella* were significantly higher in preterm infants, while the levels of *Bacteroides fragilis* were lower (but gradually increasing over time). Lastly, when accounting for clinical parameters (such as infections, NICU stay, clinical practices, and feeding regimens), the authors conclude that weight at birth seems the best explanatory variable at birth and month 12, while gestational age seemed to have more impact in the composition of preterm infant microbiota at 12 months; the insertion of a PICC line (peripherally inserted central catheter) for total parenteral nutrition administration and isolation of antibiotic-resistant bacteria, were the best explanatory variables for microbial changes at 6 and 12 months – both clinical practices have been implicated in the disruption of gut microbiota establishment (Yap *et al.* 2021). The evidence presented in the mentioned studies indicate that preterm infants might exhibit a gut microbiota dominated by potentially pathogenic microbes which, combined with invasive treatments and a compromised immune system (discussed later in chapter 2), makes them more susceptible to infections.

Maternal habits during pregnancy, namely the use of antibiotics or probiotics, can also impact the intestinal microbiota of infants. A study in an animal model demonstrated that antibiotic treatment during gestation leads to intestinal microbiota disruption (imbalance between bacterial phyla) and intestinal damage in neonatal mice (Chen *et al.* 2021). Recent studies in human babies revealed similar conclusions. Turta and colleagues demonstrated that intrapartum administration of antibiotics resulted in short-term disruption of infant gut microbiota, with a reduction in microbial richness and an increase in the relative abundances of *Clostridiaceae* and *Erysipelotrichaceae* (Turta *et al.* 2022). In contrast, maternal probiotic treatment seems to have a restorative effect on early-life gut microbiota. Korpela and colleagues (Korpela *et al.* 2018) evaluated the impact of probiotics, when taken during gestation and after birth, on infant gut microbiota, and found that the treatment increased levels of *Bifidobacteria* and decreased levels of potential pathogens (*Clostridia* and *Pseudomonadota*), although this modulation of the gut microbiota was also heavily dependent on the infant's diet.

Early-life feeding strategies may impact on the infant gut microbial colonization (Robertson *et al.* 2019). As such, an exclusive breastfeeding strategy constitutes an important source of lactic acid-producing bacteria and human milk oligosaccharides (HMO), creating an environment beneficial for the proliferation of *Lactobacillus* and *Bifidobacterium*, known probiotic genera (Ventura *et al.* 2019). In comparison, formula-fed infants exhibited a more diverse microbiota (higher number of bacterial genera) than their breastfed counterparts, possibly because formula milk contains a different array of nutrients that modulate the gut microbiota (Milani *et al.* 2017). To demonstrate the impact of an early-life diet on the gut microbiota, Brink *et al.* (Brink *et al.* 2020) compared fecal microbiota and metabolites in breastfed and formula-fed infants, with dairy-based and soy formula milk, during the first year of life. Soy-based infant formula differs from the common dairy-based formula, due to the presence of soy protein isolates instead of bovine protein isolates (Byrne *et al.* 2021). The different diet regimens lead to differences in overall microbial diversity, with breastfed infants displaying lower diversity and higher levels of *Bifidobacterium*. In a cross-sectional study, Ma *et al.* compared the microbial composition and diversity of the gut microbiota of infants fed with breastmilk or formula. It was found that despite *Bifidobacterium* being the most abundant genera in both groups, the relative abundance of potentially pathogenic bacteria (such as *Streptococcus*, *Clostridium*, and *Enterococcus*)

was higher in formula-fed babies (Ma *et al.* 2020), probably due to the low abundance of protective bacteria. To further highlight the beneficial effects of breastfeeding, Liu *et al.* evaluated the restorative effects of breastmilk in cesarean-delivered infants. The study has shown that infants born by C-section and exclusively breastfed, not only possess a gut microbiota that closely resembles one of the vaginally delivered infants, but also that breastmilk was able to restore the presence of beneficial bacteria (such as *Faecalibacterium*) and to reduce the abundance of bacterial genera typically associated with this mode of delivery (such as *Enterococcus* and *Veillonella*) (Liu *et al.* 2019). A randomized clinical trial by Embleton *et al.* evaluated different feeding regimens in the microbial composition of 120 preterm infants, to better understand if an exclusive human milk diet could impact microbial and clinical parameters in preterm newborns (particularly, when a mother's own breastmilk experiences a shortfall in supply). The participants were divided into two groups: intervention, characterized by exclusive human milk diet, in which infants were fed maternal breastmilk or pasteurized human milk, in case of shortfall of breastmilk supply; and control, in which infants were fed maternal breastmilk or artificial bovine formula, in case of shortfall of breastmilk supply. The study groups received milk fortifiers, either pasteurized human milk-derived or bovine-derived fortifiers, depending if the infant belonged to the intervention or control group. Stool samples were collected and analyzed at five timepoints: (A) baseline (following enrollment), (B) day of life 10, (C) "full feeds," (D) day of life 21–28, and (E) final sample collected before study completion (34 weeks postpartum). No significant differences among groups and throughout time were observed, and the type of feeding did not impact clinical outcomes (namely, the development of necrotizing enterocolitis and other neonatal pathologies). The only variables that did influence the bacterial profiles, at more than one timepoint, were the place of NICU stay and the intake of probiotics. In terms of microbial abundance, it was shown that infants in NICU using probiotics, displayed a higher relative abundance of *Bifidobacterium*, and it positively correlated with the number of days of mother's own milk consumption. In the intervention branch, preterm infants showed a reduced abundance of *Lactobacillus* (Embleton *et al.* 2023). The results stated in the study indicate that, while milk from human donors can be useful for infants when maternal breastmilk supply is running low, it cannot substitute it.

After 6 months, with the introduction of solid foods (weaning period), there is a significant increase in the

$\alpha$ -diversity, a diversity parameter used to evaluate the richness and evenness of microbial species of a given sample, in a certain environment (Walters and Martiny 2020). The gut microbiota shifts its composition from Pseudomonadota (previously Proteobacteria) and Actinomycetota (previously Actinobacteria) to Bacillota (previously Firmicutes) and Bacteroidota (previously Bacteroidetes) (Milani *et al.* 2017). Also, in the transition from an exclusively-breastmilk regimen to solid foods, a significant decrease in bifidobacteria was reported (Zhuang *et al.* 2019). During this period, the child's gut microbiota changes, leading to a more adult-like composition, reaching a stable composition at the age of 3. The adult microbiota is dominated by bacterial strains capable of producing short-chain fatty acids (SCFA), as well as degrading glycans and complex carbohydrates. Hence, proper nutrition during the weaning period is crucial for the establishment and maintenance of mature microbiota. Malnourishment and/or a high-fat diet, prevalent in Western societies, may lead to gut dysbiosis and growth impairment (Singh *et al.* 2020).

Other factors that may influence the composition and colonization patterns of infant gut microbiota include geographical location (closely related to cultural and dietary practices), family lifestyle (close relatives, siblings, and pets), and host genetics (Zhuang *et al.* 2019). The contribution of the host genetics to the composition of the gut microbiota remains unclear, as most conclusions are drawn from studies on twins. While some studies demonstrate that monozygotic twins exhibit a very similar microbiota, other studies debunked those theories, demonstrating no significant differences were found between identical twins (Rodríguez *et al.* 2015). Therefore, more studies are necessary.

Interaction with household members such as siblings and pets can also modulate the gut microbiota of the child. Studies have found that living with older siblings was associated with increased microbial diversity and richness and that the number of siblings was positively correlated with microbial diversity (Christensen *et al.* 2022; Laursen *et al.* 2015). Furthermore, the existence of siblings may offer protection against allergies (Christensen *et al.* 2022). Similarly, living with pets is related to increased microbial diversity and richness in the intestinal microbiota of infants, with an increased abundance of certain bacterial species, such as *Ruminococcus* and *Oscillospira* (Zoratti *et al.* 2020; Tun *et al.* 2017). Furthermore, it was found that prenatal exposure to domestic pets might be associated with a decreased streptococcal colonization and, thus, may lead to decreased risk of developing metabolic

diseases and atopy (Tun *et al.* 2017). However, additional studies are necessary to further comprehend the link between pet-infant gut microbiota and its impact on the child's health.

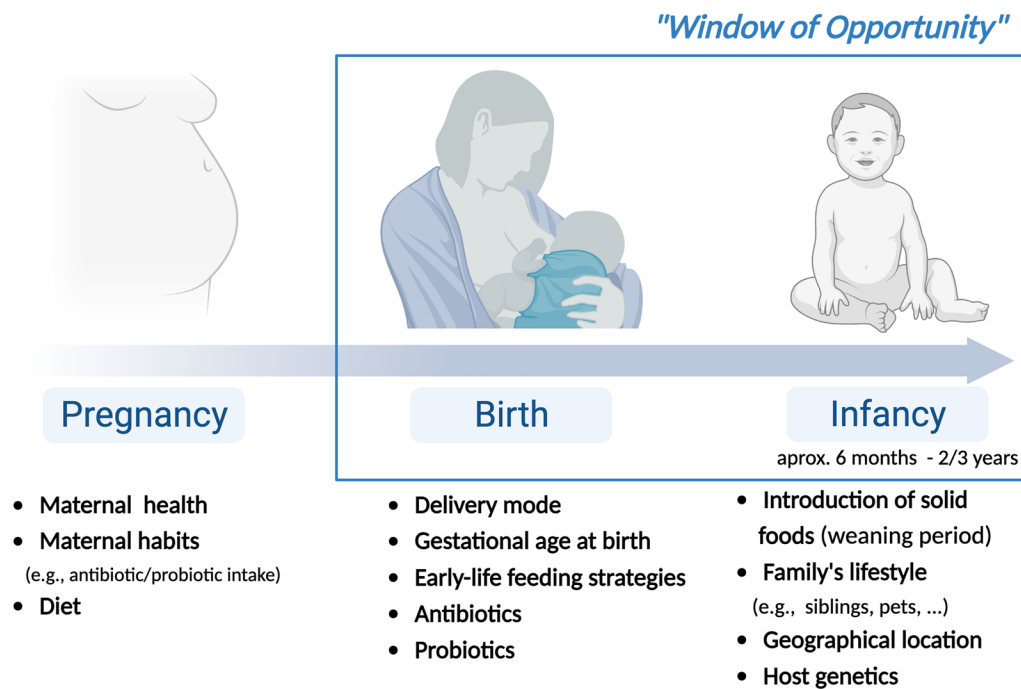
It is postulated that, after the first 1000 days of life, the microbiome is already established and maintained by the host. During this period, the microbiota and its metabolites modulate the development of the infant's immune system, offering the antigenic stimulus necessary for its maturation, through the establishment of immune tolerance, that differentiates commensal microbiota from pathogenic microorganisms (Zhuang *et al.* 2019). Of particular interest are the emerging evidence on the cellular mechanisms that trigger trained immunity or immune tolerance. Specifically, trained immunity is primed by specific Pathogen-associated molecular patterns (PAMPs) and Damage-associated molecular patterns (DAMPs), whereas immune tolerance is promoted by Gram-negative endotoxin, such as Lipopolysaccharide (LPS) (reviewed by Lajqi *et al.* 2023). Therefore, throughout the first days of life, an important "window of opportunity" is established (Figure 1), in which the interactions between the gut microbiota and the host are crucial for the development of a balanced immune system (Zhuang *et al.* 2019).

In summary, the infant gut microbiota is dominated by specific bacterial genera, depending on the development stage. After birth, the early-life gut microbiota is mainly composed of *Bifidobacterium* and *Lactobacillus*, due to maternal transmission of microbiota and breastfeeding (as these bacterial genera thrive in the presence of human breastmilk oligosaccharides (HMO)). Other bacterial genera that may be present in infant gut microbiota include *Clostridium* (despite being a potential pathogenic organism, it can remain asymptomatic in newborns), *Bacteroides*, *Enterobacteriaceae*, *Streptococcus*, and other genera found in lower relative abundances, such as *Akkermansia* (Yao *et al.* 2021; Moore and Townsend 2019).

## 2. Gut microbiota and immune system Interactions in early-life

Under normal conditions, the dynamic interactions between the gut microbiota and the host's immune system aid in the maintenance of the overall body balance. Along with intestinal and immune cells, the gut microbiota constitutes another barrier of protection, competing with pathogens for nutrients and adhesion sites in the intestinal mucosa and preventing the colonization and replication of external pathogens (Yoo *et al.* 2020). Moreover, the gut microbiota can regulate both local and systemic immune responses either





**Figure 1.** Factors that influence microbiota composition in early-life, from pregnancy to birth and infancy (created with BioRender).

directly, by interacting with adaptive and innate immune cells, or indirectly through the production of microbial metabolites (Yoo *et al.* 2020). As the infant's gut is colonized by different microbial populations, it triggers the immature immune system and induces tolerance toward this new commensal microbiota.

### 2.1. Early-Life immune system development

The immune system, alongside other protective barriers such as the skin, provides the body protection against disease and has an innate and an acquired component.

The innate immune response is nonspecific, immediate, with no immunological memory, and is mainly mediated by macrophages, neutrophils, and dendritic cells (DCs), known as professional phagocytes, and innate lymphoid cells (ILCs), mast cells, eosinophils, basophils, and natural killer cells. In turn, the acquired immune response is pathogen and antigen-specific, has a cell-mediated and a humoral component, and triggers immunological memory. The adaptive immune system is composed of T cells and B cells. Regarding T cells, there are two main subsets: CD4<sup>+</sup> T helper (Th) cells and CD8<sup>+</sup> cytotoxic T cells. CD4<sup>+</sup> T cells can be subdivided into Th1, Th2, Th9, Th17, Th22, T regulatory cells (Tregs), and follicular helper (Tfh) cells. All these subsets have distinct tasks: Th1 produce cytokines such as IL-2 (interleukin 2) and IFN $\gamma$  (interferon-gamma), responding promptly to virus and bacteria; Th2 direct their response to parasites,

through the production of IL-4 and IL-10; Th9 are central to control helminth infection and anti-tumor immunity through secretion of IL-9; Th17 have a crucial role in the response to extracellular bacteria and fungi; Th22 support mucosal immunity to microbial infection through the secretion of IL-22; Tregs are negative regulators of the immune response and protect against auto-immunity; and finally, the main role of Tfh cells is to regulate B cell immunity in the germinal centers of the lymph nodes (Wilson and Messaoudi 2015). The main function of CD8<sup>+</sup> T cells is clearing intracellular pathogens and tumors (Kurachi 2019; Wang *et al.* 2019). This T cell population, termed as cytotoxic, is divided into three major subpopulations: Tc1, with central cytotoxic activity through the secretion of granzyme and perforin, tumor necrosis factor-alpha (TNF-alpha), and IFN-gamma; Tc17 involved in mucosal immunity and production of IL-17 and defensins; and the immune suppressor Tc2 cells that produce IL-4, IL-5, and IL-13 (Annunziato *et al.* 2015; Mittrücker *et al.* 2014)). T cells can be activated and differentiated after contact with antigen-presenting cells (APCs), such as macrophages or DCs, by the presentation of pathogen-derived peptides through major histocompatibility complex class II (MHC II), in the case of CD4<sup>+</sup> T cells, or by the presentation of cellular antigens through MHC I, in the case of CD8<sup>+</sup> T cells (Yao *et al.* 2021). B cells are responsible for antibody secretion, which then coat pathogens, targeting them for opsonization, activation of the complement system, and neutralization (Gaudino and Kumar 2019).

The immune system development starts *in utero*, as early as at the 8 weeks of development, when the thymus is seeding by hematopoietic cells, and at 12 weeks of gestation the lymph nodes of the fetus are already evident. T-cell development in the thymus begins around 14 to 17 weeks of gestation and, around this time, these cells are already detected at the lymph nodes as well. On the other hand, B cells are already present in the primary follicles of lymph nodes by the 17 weeks of gestation. Conversely, DCs and circulating monocytes are only detected in the second trimester of pregnancy, increasing until the end of pregnancy. As for neutrophils, these are not present until the third trimester of pregnancy but are the predominant population of cells at birth (Wilson and Messaoudi 2015). Although throughout this period, the exposure of the fetus to live bacteria remains controversial, it is known that the presentation to diverse microbial metabolites and fragments may happen *via* the placenta (Jain 2020). Gut commensal-specific IgG antibodies may be transferred to the fetus, regulating its mucosal CD4<sup>+</sup> T-cell response to microbial antigens at birth. Interestingly, in a mouse model, maternal antibodies that only were present during pregnancy improved the transmission of microbial molecules across the placenta, which primed their pup's immune system and suppressed allergic airway diseases by increasing the number and functionality of Treg cells later in life (Thorburn *et al.* 2015).

Still *in utero*, the fetal immune system has a Th2 phenotype to prevent alloimmune responses against the mother (Abenavoli *et al.* 2019). This phenotype remains after delivery, with the infant's immune system still biased toward a Th2 phenotype, presenting low IL-2 and IFN $\gamma$  (Wilson and Messaoudi 2015). The low production of such cytokines can be due to functional differences in DCs which may prevent the differentiation of naïve CD4<sup>+</sup> T cells toward Th1 (Wilson and Messaoudi 2015). However, after multiple pathogenic encounters and in a time- and age-dependent manner, the infant switches toward a Th1 polarization, promoting a pro-inflammatory profile, with negative consequences in the child's long-term health (Abenavoli *et al.* 2019).

During delivery, infants receive "a bacterial boost" mainly from the mother, exposing the immature immune system of the newborns to a significant microbial load (Abenavoli *et al.* 2019). After delivery, the immune system of the newborn is still functionally immature and is markedly modulated to avoid excessive inflammatory responses. For this reason, it is observed a dampening of the immune system mechanisms, characterized by a decrease in the complement

function, decrease in neutrophils amount and functions, decrease in the production of pro-inflammatory cytokines by APCs (IL-1 $\beta$ , tumor necrosis factor (TNF)- $\alpha$ , and IL-12p70), and an increased expression of inhibitory receptors by NK cells, such as NKG2A/CD94 (Esteve-Solé *et al.* 2018; Wang *et al.* 2007). Simultaneously, CD8 T cells present low activity, and monocytes and macrophages still show immaturity (Méndez *et al.* 2021).

Likewise, B cells are mostly naïve at birth and their ability to respond is limited possibly due to their immaturity, poor B cell repertoire, or reduced strength of B cell receptor (BCR) signaling (Wilson and Messaoudi 2015; Basha *et al.* 2014). Additionally, neonates have underdeveloped germinal centers in lymph nodes and spleen and low expression of BCRs, resulting in low levels of primary IgG responses to infections and vaccines (Basha *et al.* 2014). Therefore, neonates exhibit an increased susceptibility to infections because of the immaturity of their lymphocytes, low numbers of effector-memory T cells, low Th1 cytokine secretion, and reduced strength of BCR signaling.

In this context it is of note that preterm infants, compared with term infants, have an underdeveloped immune system, characterized by diminished innate and adaptive immunity. They have a smaller pool of monocytes and neutrophils, and the compromised capacity of these cells to eliminate pathogens, coupled with decreased cytokine production, restricts T cell activation and undermines the ability to combat bacteria and detect viruses within cells (Melville and Moss 2013). In normal conditions, the adaptive immune system is only completely developed in the early childhood, meaning that the neonates strongly rely on innate immune response, which in the case of preterm infants is a critical issue, since they have an immature innate immune system (Melville and Moss 2013). Moreover, antigen-specific IgG are abundantly transferred across the placenta from the maternal circulation, particularly after the 32<sup>nd</sup> week of gestation, and the transfer increases with fetal age, which can result, in preterm infants in lack of pathogens opsonization and deficiencies in phagocytosis (van den Berg *et al.* 2011).

Since the newborn adaptive immune system is exclusively constituted by naïve T and B cells, during the first 6 months of life, maternal antibodies acquired *in utero* and breastmilk provide additional protection against pathogens in the GI and respiratory tract (Wilson and Messaoudi 2015). Indeed, the feeding strategy may also impact early-life immunity by modulating the production of microbial metabolites, with breastfed infants displaying higher concentrations of fecal butyric acid (derived from the metabolism of SCFA and able to increase regulatory T cell

differentiation), d-sphingosine (involved in immune cell trafficking) and betaine (inhibits inflammatory responses) (Brink *et al.* 2020). Furthermore, breastmilk also provides IgA, the main immunoglobulin in mucosal protection, enabling a tolerant and balanced immune system (Milani *et al.* 2017). The secretory IgA (sIgA) present in the breastmilk is produced by plasma cells in the mammary gland but originally from the gut of the mother. Therefore, the specificity of the sIgA is modulated by maternal exposure to her enteric bacteria, both commensals, and pathogens, therefore protecting from the expansion of the latter while the child's immune system is maturing (van den Elsen *et al.* 2019). Furthermore, sIgA also seems to shape the gut microbiota of the child with a long-lasting effect, which is fundamental to prevent excessive expansion of pro-inflammatory microbial taxa, and in the modulation of microbial gene expression and metabolic function (van den Elsen *et al.* 2019).

The number of immune cells varies in different age groups (Méndez *et al.* 2021; Valiathan *et al.* 2016). Lymphocytes, including CD4<sup>+</sup> T cells and B cells, appear to decrease significantly with age, whereas neutrophils and CD8<sup>+</sup> T cells increase in adulthood, and NK cells increase in adolescence (Méndez *et al.* 2021; Valiathan *et al.* 2016). Throughout infancy and early childhood, the Th phenotype changes to a Th1 phenotype, potentiating macrophage activation and cellular immunity (Wilson and Messaoudi 2015). At the age of 2, DCs start producing the cytokine IL-12p70, which then stimulates the Th1 response. Furthermore, with further antigen exposure, T cell response increases, and cytotoxic and Th cells develop memory toward the antigen (Méndez *et al.* 2021).

Innate lymphoid cells (ILCs) are another component of the innate immune system, and that has an important role in neonatal immunity. In adulthood, ILCs originate from a common lymphoid precursor (CLP) located in the bone marrow, which originates a common helper-ILC precursor (CHILP), eventually differentiating in different subsets, depending on their cytokine expression profile (namely, ILCs group 1, group 2, and group 3) (Ganal-Vonarburg and Duerr 2020). In early-life, ILCs derive from a progenitor located in the fetal liver, but have been found in other sites of the fetal environment, including the secondary lymphoid organs (such as the mesenteric lymph nodes and Peyer's patches) and the intestine. Despite the gaps in the current literature, studies in rodent models claim that a different subset of ILCs, the lymphoid tissue inducer cells (LTi), have a central role in the proper development of SLOs, as reviewed + (Mendes *et al.* 2020). Moreover, it is suggested that ILCs can confer

protection to the newborn, as it transitions from the sterile womb to a microbially-rich environment, and establishes the tolerance system which distinguishes between commensal and harmful microbes (Yu *et al.* 2018).

In sum, the first 1000 days of life are fundamental not only to the microbiome establishment, but also to the concomitant development and maturation of the immune system and, consequently, to the interplay between both. Hence, this period is considered to represent a microbiological and immune 'window of opportunity' during which any event will have a pivotal impact on the metabolic, immunological, and microbiological priming, which may later affect human health (Selma-Royo *et al.* 2019).

## 2.2. Gut microbiota and immune system Interactions

The complex balance between host immunity and gut microbiota is established when the commensal microorganisms interact with intestinal epithelial cells (IEC). The immune response begins with the recognition of microbe-associated molecular patterns (MAMPs) by pattern recognition receptors (PRRs), located on IECs or DCs, which can then recruit activated B and T cells. PRRs, which can include Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors, when activated by MAMPs, induce the production of antimicrobial peptides, such as regenerating islet-derived protein III-gamma (RegIIIγ), and immunological mediators such as IL-18, IL-33, IL-25, and tumor growth factor-β (TGF-β) which, consequently, promotes the development tolerogenic macrophages (producers of high levels of IL-10) and DCs, which stimulate the differentiation of Tregs (Maranduba *et al.*, 2015; Thaïss *et al.* 2016). In the specific case of TLRs, they can be activated by a wide variety of microbial antigens (including LPS, peptidoglycan, and flagellin) and trigger a signaling cascade that results in the activation of the NF-κB transcription factor, which regulates the expression of cytokines, chemokines, and of other immunological mediators. A known example of the role of TLRs in gut eubiosis (balanced gut microbiota) is the model of polysaccharide A (PSA) of *Bacteroides fragilis*. PSA can be detected by TLR2/TLR1 heterodimer in collaboration with Dectin (a C-type lectin PRR), promoting the activation of anti-inflammatory genes. Furthermore, Dectin-1 can control gut immunity by altering the microbiota pattern, leading to Treg differentiation (Al-Rashidi, 2022). Moreover, PRRs can also contribute to the elimination of pathogenic microorganisms, through the activation of the



inflammasome-forming NLR family CARD-domain containing protein 4 (NLRC4) which triggers the detachment of the infected epithelial cells when detected as infected by a pathogen (Thaiss *et al.* 2016).

Considering the mechanism of microbiota recognition and the importance of the early-life microbiota in immune system priming, it is important to highlight a recent study by Wampach *et al.* in which it assessed the immunostimulatory potential of maternal microbiota transferred to infants born through vaginal or cesarean delivery. This study reported that fecal LPS isolated 3 days after vaginally-delivered neonates induced higher levels of cytokines in monocyte-derived DCs, compared with fecal LPS from cesarean-delivered neonates (Wampach *et al.* 2018). Since LPS is recognized by TLR-4 on the membranes of intestinal epithelial cells and it stimulates components of the immune system, these results suggest that disturbances in the initial microbiota inherited by the mode of delivery may impact the immune system stimulation and, thus, the immune response of the infant (Jašarević and Bale, 2019). Moreover, a recent study in mice observed that vaginally-delivered offspring acquired immune tolerance *via* spontaneous activation of the intestinal epithelial cells and acquired resistance to LPS shortly after delivery, whereas C-section-born pups and TLR4-deficient mice did not (Lotz *et al.*, 2006).

### 2.2.1. Gut microbiota and innate immune system Interactions

Within the gut epithelium, specialized cell types are involved in immune recognition. At the gut-associated lymphoid tissue (GALT), Peyer's patches, isolated lymphoid follicles (ILFs), and epithelial M cells are part of the local immune system, sampling antigens from the lumen and presenting them to APCs located under the epithelium. Enteroendocrine cells, by their side, act in the local immune system through the production of glucagon-like peptide 2 (GLP-2), involved in the regulation of the innate immune response, by controlling the expression of antimicrobial peptides (AMPs) (Maranduba *et al.*, 2015). Additionally, in the lamina propria, the commensal microbiota can also stimulate and interact with innate lymphoid cells (ILC), tissue resident cells particularly abundant in the intestinal mucosa. Despite some similarities with Th cells, ILCs respond faster to pathogens, by presenting antigens to Th cells and promoting their differentiation and activation, and acting as essential players in the maintenance of intestinal barrier integrity. Upon damage to the epithelium, ILCs are activated to restore barrier function (Zheng and Zhu 2022). The commensal microbiota induces the

secretion of intestinal cytokines, and in turn, ILCs can react to the gut microbiota by altering their structure, with consequences on gut immunity (for example, promoting the production of antimicrobial peptides by IECs) (Han *et al.*, 2019).

Other immune cells pivotal to the initiation of the primary immune response are intestinal DCs, by limiting the reactivity toward the commensal gut microbiota and by recognizing potential pathogens (D'Amelio and Sassi, 2018). Intestinal DCs, typically found in the GALT, are continuously exposed to luminal antigens and thus, in order to distinguish between innocuous microbiota and pathogenic microbes, they sample the luminal content (Stagg 2018; Owen and Mohamadzadeh 2013). These cells have distinct ways of antigen recognition and capture: they can extend dendrites across the epithelial layer and capture translocated IgA immune complexes, or sample the luminal space through M cells, which internalize microorganisms and deliver to DCs (Stagg 2018; Swiatczak and Rescigno 2012). Activation of gut DCs is facilitated by PRRs, such as TLRs. Concerning DC interaction with gut microbiota, the typical response is tolerance to prevent inflammation, a mechanism known as oral tolerance, a state of non-response toward antigens from food (Sun *et al.* 2020). The main location for this process is within the mesenteric lymph nodes (MLNs), in which DCs are strong promoters of tolerance. Additionally, intestinal DCs can promote IgA class switching in B cells, further enhancing the maintenance of gut homeostasis (Tezuka and Ohteki 2019). For instance, bacterial products, and certain species of probiotics have been shown to promote tolerance in DCs, simply by attaching to their surface. A few examples include the interaction between intestinal DCs and *Lactobacillus acidophilus* NCFM (a food supplement), in which the bacteria was able to promote the secretion of IL-10, an anti-inflammatory cytokine (Swiatczak and Rescigno 2012). Besides live bacteria, bacterial products can also induce a tolerogenic profile in intestinal DCs. Wang *et al.* (2006) showed that, when exposed to the bacterial product PSA, derived from *Bacteroides fragilis*, intestinal DCs promote inducible nitric oxide synthase (iNOS), to produce nitric oxide, which appears to exert an impact in the maintenance of intestinal homeostasis (Tezuka and Ohteki 2019; Wang *et al.* 2006).

### 2.2.2. Gut microbiota and adaptive immune system Interactions

Bacterial-loaded DCs can also induce the differentiation of B cells into IgA<sup>+</sup> plasma cells, leading to IgA secretion, IgA coating, and opsonization of the pathogen for

elimination, which can occur through T-cell-dependent or independent mechanisms (Tezuka and Ohteki 2019). This antibody production, affinity maturation, and class switch recombination require complex interaction between DCs and B cells in the Peyer patches, dependent on the secretion of TGF- $\beta$  by ILCs. Still regarding the interaction between B cells and the gut microbiota, and as previously mentioned, the low production of sIgA in newborns is compensated by the presence of these antibodies in the mother's breastmilk. As so, breastmilk IgA plays an important role in modulating the gut microbiota in early-life by driving microbial colonization and immune system maturation and priming (Thorburn *et al.* 2015). As the neonate gut begins to be progressively colonized by different species, the immune system responds by producing endogenous sIgA, which will then modulate the composition of the microbiota (Thorburn *et al.* 2015). The mechanisms behind the control and proliferation of commensal bacteria are still to be unveiled, but it is hypothesized that it might be related to the ability of sIgA to bind to bacteria, promoting changes in the regulation of gene expression which will then influence their metabolic processes and the biogeography of the gut (Kato *et al.*, 2014).

Regarding T cells and microbiota, the most studied CD4<sup>+</sup> T cell subtypes are Th17 and Treg. In the case of Th17, in response to stimuli (such as segmented filamentous bacteria – SFB), naïve CD4<sup>+</sup> T cells can migrate to the intestinal lamina propria and differentiate into IL-17A-producing Th17 cells. Consequently, the cytokines produced by these cells (IL-17A, IL-17F, IL-22) stimulate IECs to produce AMPs, helping to preserve a non-inflammatory state of the intestinal barrier (Wang *et al.* 2019; Ivanov *et al.*, 2009; Weaver *et al.* 2013). On the other hand, Treg cells located in the intestinal lamina propria have a fundamental role regarding tolerance toward commensal microbiota. For instance, ROR $\gamma$ t<sup>+</sup> Tregs population located in the colon seems to be expressed in a microbiota-dependent manner. In germ-free mice, this population seems to decrease, and, during weaning, the generation of ROR $\gamma$ t<sup>+</sup> Tregs is associated with a decreased susceptibility to allergic inflammation later in life. Moreover, the induction of peripheral Treg cells can suppress abnormal inflammatory responses (Wiertsema *et al.* 2021). Overall, intestinal homeostasis is maintained by a balance between the effector T cells and Treg cells, which mediate immune responses and confine excessive immune activation, respectively (Wang *et al.* 2019). Likewise, some probiotic *Lactobacillus* strains improve intestinal inflammation by modulating the ratio between Tregs and Th17 cells (Wang *et al.* 2017).

The production and release of gut microbial metabolites, such as bile acids, branched-chain amino acids, and trimethylamine N-oxide, can also greatly impact the host immune response, influencing inflammatory signaling and interactions with immune cells (Agus *et al.*, 2021). Certain gut bacteria, such as *Faecalibacterium prausnitzii* and *Roseburia intestinalis* (known probiotics), can generate microbial metabolites through the anaerobic fermentation of complex carbohydrates (dietary fibers and resistant starch), namely SCFA (Silva *et al.* 2020). Shortly after their production, SCFA are absorbed by colonocytes, and then transferred to the liver, where they are used as an energy supply for hepatocytes, with the exception of acetate, which is oxidized. A small fraction of SCFA can also be carried through the systemic circulation to other tissues (Silva *et al.* 2020). Being the most abundant microbial-derived metabolites, SCFA influences gut health through several mechanisms, specifically, maintenance of gut barrier integrity, mucus production, and protection against inflammation and pathogens. These mechanisms occur due to signaling triggered by SCFA, which can bind to G protein-coupled receptors (GPCRs), expressed in several cell types, or through the inhibition of histone deacetylases (HDACs), a mechanism often linked to immune tolerance and anti-inflammatory phenotype, aiding in the maintenance of immune homeostasis (Yoo *et al.* 2020; Silva *et al.* 2020). Nevertheless, the activation of these receptors will result in different outcomes, depending on the type of cells involved. For example, SCFA, particularly butyrate, influences the systemic immune response through the control of the differentiation process of T cells, thus, influencing the adaptive immune response. These microbial metabolites can impact the differentiation of T cells either in Th1, Th2, and Th17 cells, or into Tregs. Moreover, SCFA can also reduce inflammation, regulating the expression of pro-inflammatory cytokines (such as IL-6, IL-12, and TNF- $\alpha$ ) by activating macrophages and DCs (Yoo *et al.* 2020). SCFA can also lead to the induction of regulatory B cells, inhibiting the generation of Th17 cells, which may play a role in preventing autoimmune disorders or gastrointestinal diseases such as inflammatory bowel disease (IBD) (Wiertsema *et al.* 2021). Furthermore, the commensal bacteria can impact the innate immune response, for example, through lymphoid stimulation in the spleen, activation of macrophages, and stimulation of the maturation process of NK cells (Wiertsema *et al.* 2021).

Of note are the observations from germ-free mice demonstrating that gut microbiota colonization in early-life is essential for optimal immune development, as these animals presented underdeveloped mucosal

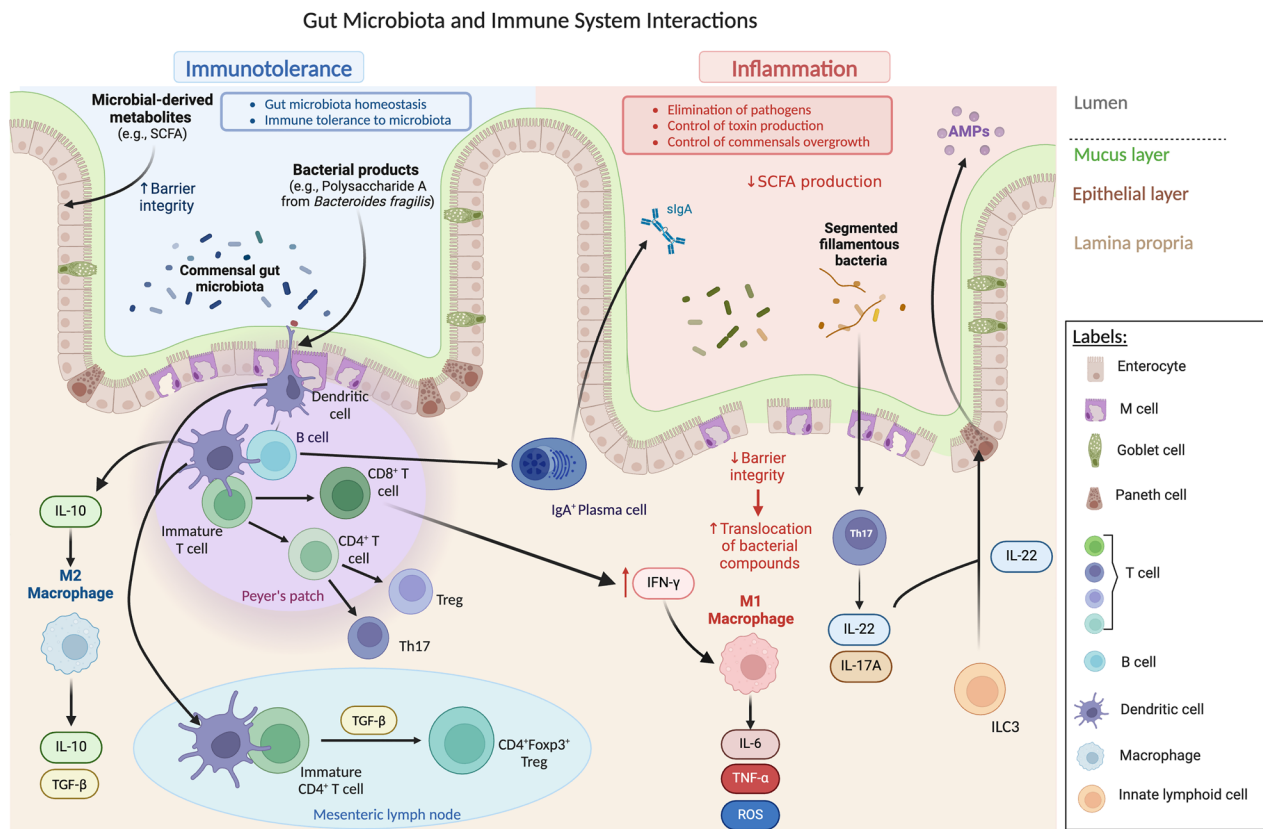
immunity, reduced number of immune cells as IgA-producing plasma cells, CD4<sup>+</sup> and CD8<sup>+</sup> T-cells, and reduced capacity of resisting to pathogenic bacteria (Sommer and Bäckhed 2013). Therefore, early-life gut colonization is a sequential process that influences the maturation and development of the child's immunity, such as through the production of SCFA (Silva *et al.* 2020; Yang *et al.* 2020) or the control of proliferation and differentiation of T and B cells (Tanaka and Nakayama 2017).

Overall, the interactions between gut epithelial and immune cells contribute to the tolerogenic state of the intestinal environment (Wang *et al.* 2019). Under physiological conditions, the gut microbiota contributes to intestinal tolerance *via* sIgA production and Treg differentiation, and tolerogenic DCs and macrophages contribute further to this, *via* IL-10 secretion. Gut microbiota, SCFAs, and IL-21 secreted from Tfh cells contribute to the secretion of specific sIgA, which will then opsonize the gut commensal bacteria to control their proliferation and toxin production. Commensal bacteria components induce further Treg and B cell production and promote IFN $\gamma$  secretion from CD8<sup>+</sup> cells. On the other hand, sIgA and tolerogenic DCs

negatively regulate the stimulation of Th17 cells, inhibiting a strong pro-inflammatory response against commensal bacteria. Tregs also downregulate DCs and Th17 cells by producing TGF- $\beta$  (Wang *et al.* 2019). In this scenario, the intestinal balance is well maintained (Figure 2).

### 3. Early-Life obesity-associated gut dysbiosis and alterations in the immune system

During early-life, the interplay between the infant's intestinal microbiota and the immune system significantly influences each other development: the colonization of commensal microbes affects the maturation of lymphoid tissues and lymphocytes, while the host's immune response influences the selection and maintenance of commensal microbiota, fostering a stable equilibrium and ecological balance among microbial communities (Hong and Medzhitov, 2023). For example, loss of microbial diversity leads to increased serum IgE production in mice which could be rescued by neonatal but not adult microbial colonization (Cahenzli *et al.*, 2013). At the same time, infant's intestinal microbiota is highly plastic and shaped by several external



**Figure 2.** Interactions Between intestinal commensal microorganisms and the immune system. In the figure are depicted the immune response to both pathogenic and nonpathogenic microorganisms that will trigger an inflammatory response or immunotolerance, respectively (created with biorender).

factors, including the maternal microbiota. During this period of development, the mother plays a crucial role in the establishment of early-life gut microbiota, since mothers vertically transmit their microbiome and their metabolites to the offspring maybe *in utero*, but certainly during delivery and breastfeeding (Soderborg *et al.* 2016). Therefore, the mother impacts the composition of the infant's gut microbiota, as well as its immunity. The composition of the maternal microbiota can vary depending on different factors such as diet, exposure to antibiotics, systemic health status, and diseases such as obesity, which in turn, affect the infant's gut microbiota (Neff *et al.* 2018; Arrieta *et al.*, 2015).

Obesity has become a worldwide problem, with over 500 million people suffering from this condition according to the World Health Organization. Obesity is often associated with other comorbidities, such as type 2 diabetes and cardiovascular disease (Milano *et al.* 2022). High-calorie diets and sedentarism might have contributed to the steady rise of these numbers. Still, obesity is a complex disease, influenced not only by the environment, but also by the genetic makeup of the host (genetic polymorphisms) and, as unveiled more recently, by the gut microbiota (Milano *et al.* 2022). Altered gut microbiota can contribute to obesity by increasing energy intake, inflammation, and alterations in metabolic pathways (Kincaid *et al.*, 2020). It is estimated that maternal obesity affects two out of five pregnancies, representing a serious health issue since maternal obesity can influence the health of the infant, which is already vulnerable to external threats in early-life (Di Gesù *et al.*, 2021).

### 3.1. Obesity and gut microbiota

The link between obesity and gut microbiota has been studied in animal models and human patients. Menni *et al.* observed that patients with a more diverse gut microbiota were less prone to develop long-term weight gain, suggesting a preventive effect of the gut microbiota (Menni *et al.* 2017). Other studies focused on the differences observed in the Bacillota/Bacteroidota ratio between obese and lean individuals (Kasai *et al.*, 2015). However, there is some controversy in using the Bacillota/Bacteroidota ratio as a marker for obesity since discrepancies were reported in other studies in which obese patients showed decreased Bacillota/Bacteroidota ratio, as reviewed (Magne *et al.*, 2020). Another factor that contributes to these inconsistencies is related to the metabolic endotoxemia hypothesis, which proposes that increased adiposity and development of low-grade inflammation could be associated with the dissemination of LPS – the theory

is at odds with decreased levels of Bacteroidota observed in obese patients since this phylum is mainly composed of Gram-negative bacteria (rich in LPS) (Magne *et al.*, 2020). These divergences could also be related to the experimental procedure applied in different studies, such as the number of participants and the methods used, or even the heterogeneity between participants (Magne *et al.*, 2020).

Additionally, scientific evidence suggests that another putative mechanism for this causal relationship between the gut microbiota and obesity may be a higher energy extraction from the diet by the gut microorganisms. The gut microbiota metabolizes certain compounds from the diet that would otherwise not be digested, such as some carbohydrates and fibers. These are then converted by the intestinal microbiota into SCFA, which, in turn, correspond to 10% of the human daily energy intake and are essential for colon and liver cells. It has been found that when lean and obese adults have a diet with excessive calorie content, lean subjects lose more energy through stool than obese subjects (Jumpertz *et al.*, 2011). But a core theme in the link between obesity-microbiota is that diet has a deep impact on the composition of the intestinal microbiota and, consequently, on the host health. A Westernized diet, rich in saturated fats and poor in fiber, can cause a shift in the individuals gut microbiota, leading to a reduction in the abundance of beneficial microorganisms (dysbiosis) and increasing inflammation, a profile often associated with the development of metabolic disorders such as obesity (Kim *et al.*, 2019).

The bidirectional connection between gut microbiota and the central nervous system, known as the microbiota-gut-brain-axis (MGBA), has been extensively studied in recent years as a novel route to control obesity (as reviewed by (Longo *et al.*, 2023)). A few studies have highlighted the key influence of gut microbes, and its metabolites, on the vagal nerve, particularly in the regulation of eating behaviors and development of obesity (Asadi *et al.*, 2022; Sen *et al.* 2017). The MGBA has been explored in the context of early-life and brain development, since this process occurs in parallel with the maturation of the gut microbiota, and it is influenced by environmental factors, including diet, lifestyle and, maternal health (Cerdó *et al.*, 2023). Obesity-induced maternal gut-dysbiosis has been associated with behavioral complications in children, with recent studies indicating that maternal cardiometabolic disease and gut dysbiosis, were linked to negative psychiatric outcomes in children (such as behavioral issues and attention deficits), and a disturbed infant gut microbiota composition, with increased prevalence of bacterial



species positively correlated with psychological conditions in the offspring (Nieto-Ruiz *et al.* 2023; Liu *et al.*, 2021). Although the maternal gut microbiota has been proposed as a possible mediator between maternal obesity and infant brain development, a definite mechanism is yet to be determined. Research suggests that an disturbed transfer of metabolites (including microbial SCFA) and nutrients from mother to fetus during gestation, and a chronic inflammation state (in part, due to increased levels of LPS caused by the dysbiotic gut microbiota), could negatively impact fetal brain development, eventually leading to impairment of behavioral and cognitive pathways (Di Gesù *et al.*, 2021; Nieto-Ruiz *et al.* 2023; Sajdel-Sulkowska 2023)).

### 3.2. Maternal role on offspring obesity

The influence of maternal obesity in the child's future health may start even before delivery, as dietary, metabolic, and microbial changes during pregnancy may already predispose metabolic changes in the offspring (Rubini *et al.* 2022). Maternal obesity is associated with irregular feto-placental function and an increased body fat percentage and insulin resistance during gestation (Beckers *et al.*, 2024). Regarding maternal diet, it was also observed that a high-fat diet during pregnancy is linked to gut dysbiosis in primate infants, characterized by reduced diversity at 1 year of age even after switching to a healthy diet at the time of weaning (Ma *et al.*, 2014). Kimura *et al.* found that pups born to germ-free mothers (who consumed a high-fat diet) and/or mothers fed a low-fiber diet, exhibited a pronounced obesity phenotype, characterized by an increase in body weight and food consumption (Kimura *et al.*, 2020). Furthermore, infants born to mothers with high-fat intake during pregnancy were found to have lower levels of *Bacteroides*, which persisted from birth until 6 weeks of age (Chu *et al.*, 2016).

Another study by García-Mantrana and colleagues centered around maternal BMI and diet, and its impact on the offspring anthropometric measures, at 1 month and 18 months after birth. Firstly, the study describes that maternal microbiota could be divided into two clusters: Cluster I, dominated by *Prevotella*, and Cluster II with a prevalence of *Ruminococcus*. Moreover, maternal microbiota composition was diet-dependent: for instance, increased consumption of fibers, omega-3, and polyphenols (associated with a vegetarian diet) was linked to an increased abundance of *Christensenellaceae*, *Dehalobacterium*, and *Eubacterium*, and low levels of *Dialister* e *Campylobacter*. The second part of the study stated that maternal clusters were associated with neonatal gut microbiota

and growth measures (namely BMI and Weight for Length - WFL), but dependent on the mode of delivery. Thus, infants from Cluster I and born by c-section presented higher z-scores at 18 months, and a higher risk of weight gain; infants from Cluster II (who also showed the highest levels of exclusive breastfeeding), showed lower BMI and WFL at the two timepoints. The authors concluded that infant anthropometric data (particularly at 18 months) was strongly influenced by maternal diet, maternal microbiota clusters, and mode of delivery (García-Mantrana *et al.*, 2020). Recently, Dreisbach and team evaluated the link of pre-pregnancy BMI and maternal gut microbiota, with weight at birth. Following the analysis of 102 fecal samples of pregnant women in the second trimester, and after adjustment for confounding factors (antibiotic use and total weight gain during gestation), the researchers found that pre-pregnancy BMI and the component PC3 of the maternal microbiota (when controlled for the glucose levels) were predictive variables of neonatal weight. Within the microbial consortium that comprised the PC3 component, the probiotic *Lactobacillus kefir*, and respective virus *Lactobacillus phage 3 SAC12*, were the highest contributors to changes in neonatal weight (adjusted to gestational age). The researchers also observed several microbial taxa, commonly isolated from freshwater sources, represented in the PC3 component, but there is insufficient data exploring the impact of water quality and microbiota changes in the early-life (Dreisbach *et al.*, 2023).

Moreover, the researchers verified that SCFA produced by the maternal microbiota can confer resistance to obesity to the offspring, by interacting with GPR41 and GPR43 receptors (G-protein coupled receptors), during fetal development. The activation of these receptors during embryonic maturation aids in the maintenance of energy homeostasis by promoting the differentiation of sympathetic neuronal, enteroendocrine, and pancreatic cells (Kimura *et al.*, 2020). More recently, in a randomized controlled trial, Sugino and colleagues found that women with gestational diabetes mellitus that consumed a diet rich in complex carbohydrates with reduced fat had an advantageous impact on their microbiome, with increase in the probiotic family *Bifidobacteriaceae*, specifically *B. adolescentis*, enhancing the diversity in the infant gut microbiome, during the first four months of life, while mitigating the presence of opportunistic pathogens that could influence obesity and immune system development (Sugino *et al.* 2022). Thus, the effect of maternal diet exposure, metabolism, and microbiota during gestation may modulate the composition of the



microbial community of the child, with long-lasting effects.

The transmission of microbiota between mother and child with the potential to promote obesity has been suggested as a possible route of intergenerational transmission of obesity, with maternal weight being the factor unrelated to the child that most influences the development of obesity in childhood and throughout life (Skrypnik *et al.* 2019). Stanislawski *et al.* followed up a cohort of 165 children 4, 10, 30, 120, 365, and 730 days after delivery and at 12 years of age. The authors observed that, in early-life, taxa within the gut microbiota that best predicted later childhood body mass index (BMI), substantially overlapped with the maternal taxa most strongly associated with overweight and obesity, namely *F. prausnitzii* and *Ruminococcaceae*. In other words, certain bacterial taxa associated with the BMI of children later in life might derive from bacterial taxa found in the mother's gut microbiota, and that is often associated with obesity. The results show an association between the infant gut microbiota and later BMI, and they offer preliminary evidence that the infant gut microbiota, particularly at 2 years of age, may have the potential to help identify children at risk for obesity (Stanislawski *et al.* 2018). Singh *et al.* considered birth mode and pre-pregnancy BMI when analyzing the gut microbiome composition from fecal samples from 6-week-old infants. In the vaginal-delivery group, maternal overweight or obesity was associated with higher infant gut microbiome diversity and higher relative abundance of 15 operational taxonomic units (OTUs), including the overrepresentation of *Bacteroides fragilis*, *Escherichia coli*, *Veillonella dispar*, and OTUs in the genera *Staphylococcus* and *Enterococcus* (Singh *et al.* 2020). Another recent study reported that high maternal BMI is associated with a lower abundance of butyrate-producing bacteria (such as *Ruminococcus*, *Turicibacter*, and *Roseburia*) in their children 1 month after delivery and that higher microbial diversity at this stage may predict higher adiposity later in life (Gilley *et al.*, 2022). Additionally, at 6 months, infants from obese mothers had a lower abundance of bacteria from the family *Lachnospiraceae*, and, at 12 months, these infants had a lower abundance of *Desulfovibrionaceae*, *Porphyromonadaceae*, and an increased abundance of *Enterobacteriaceae* (Gilley *et al.*, 2022).

Since early-life represents a critical window for immune stimulation, maternal obesity may reprogram the neonatal immune system (Neff *et al.* 2018). For instance, a study that assessed umbilical cord blood samples from babies born from lean mothers versus

babies of obese mothers reported that the latter had fewer eosinophils and CD4<sup>+</sup> T helper cells, reduced monocyte and DCs responses to TLR ligands, and increased levels of IFN- $\alpha$ 2 and IL-6 (Wilson *et al.* 2015). More recently, a study comparing cord blood leukocytes from pregnancies with and without obesity demonstrated that pregnancy obesity is linked to a unique pattern of gene expression and DNA methylation in cord blood monocytes, in leptin-related genes, suggesting that this feature serves as a distinguishing characteristic of neonatal monocytes born to mothers with obesity (Krause *et al.*, 2023). Moreover, similar transcriptional characteristics were reproduced in neonatal monocytes from the cord blood of healthy women subjected to pro-inflammatory stimuli. As such, this study indicates that the leptin pathway influences the inflammatory response in neonates and contributes to the programming of fetal and neonatal monocytes, a process influenced by pre-pregnancy or gestational obesity (Krause *et al.*, 2023). In the same line, other authors showed that the maternal triglycerides levels are associated with, cord blood leukocytes epigenetic differences in immune and lipid metabolism-associated genes, which in turn was associated with child adiposity at 4–6 months and 4–6 years (Waldrop *et al.* 2024), highlighting the role of the epigenetic mechanism as a link between healthy conditions of the mother and the offspring.

The importance of maternal-associated mechanism of epigenetic regulation in the child is also emphasized by two studies with non-human primates models subject to western-style diet, associated with obesity (Nash *et al.* 2023; Sureshchandra *et al.* 2023). However, while in one study a mother western-style diet was associated with increased chromatin accessibility in inflammatory genes of juvenile's hematopoietic stem and progenitor cells and bone marrow-derived macrophages (Nash *et al.* 2023), the other described that pre-gravid obesity is associated with reduced chromatin accessibility and lack of chromatin remodeling in umbilical cord monocytes, which resulted in attenuated response to bacterial and virus pathogens stimulation (Sureshchandra *et al.* 2023). The blunt reaction was not only observed in umbilical cord monocytes but also in peripheral blood monocytes and tissue-resident macrophages obtained from animals born from obese mothers, fed with a high-fat diet (Sureshchandra *et al.* 2023).

Another study in a human cohort verified that maternal obesity was associated with a higher level of plasma superoxide-dismutase activity, IL-6, and IL-7 in neonates (Hernández-Trejo *et al.*, 2017). A study by Enninga *et al.* (2021) reported that newborns from

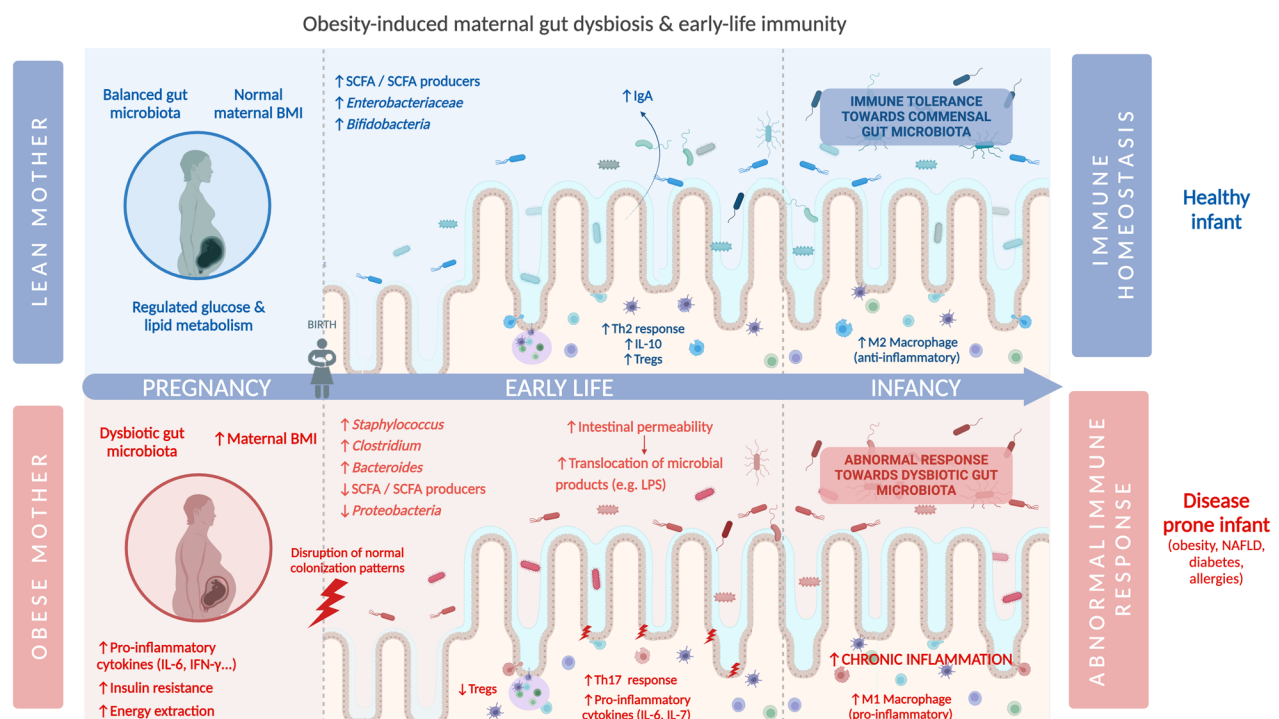
women with high BMI presented significantly increased levels of CD4<sup>+</sup> T cells and decreased myeloid cell populations, as well as increased concentrations of IL-12p40 and macrophage-derived chemokine (Enninga *et al.*, 2021). However, it remains to be clarified if these changes in immune and inflammatory profiles persist during child development. Interestingly, with the information that maternal obesity correlates with increased susceptibility to obesity and nonalcoholic fatty liver disease (NAFLD) in offspring, Soderborg and colleagues explored the effect of colonization of germ-free mice with stool microbes from 2-week-old infants from obese or lean mothers, (born vaginally, exclusively breastfed, and without exposure to antibiotics after delivery) (Soderborg *et al.* 2018). Colonization resulted, in the first animal group, in increased intestinal permeability, reduced macrophage phagocytosis, and decreased cytokine production suggestive of impaired macrophage function. Moreover, feeding the animals with a western-style diet resulted in excess weight and accelerated NAFLD in mice colonized with the microbiota from infants from obese mothers first (Soderborg *et al.* 2018). These results highlighted that the early gut dysbiosis have a clear impact in metabolism and inflammation, and may impact the proper myeloid development (Figure 3).

The importance of the initial seeding of early-life gut microbiota with maternal microbes in the development of the immune system of the child may be the

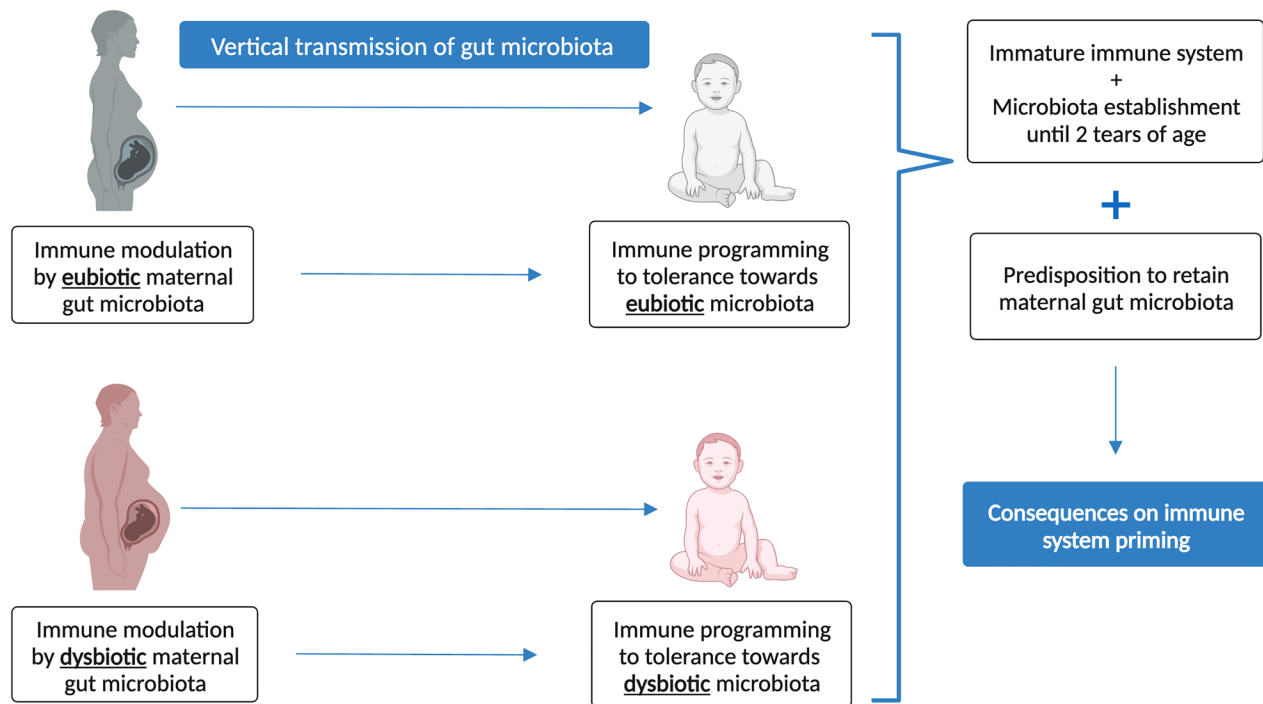
reason why maternally transmitted strains are more likely to adapt and persist in the gut of the infant than non-maternally acquired strains (Azevedo *et al.*, 2020; McDonald and McCoy 2019; Tamburini *et al.* 2016) (Figure 4). In the case of obese mothers, it is possible to hypothesize that, if the maternal microbiota is vertically transmitted to the child and if this microbiota is already dysbiotic, combined with the fact that the immune system of the infant is influenced by the mother in early-life (e.g. *in utero* transmission of immune cells, immunoglobulins, and cytokines stimulated with maternal gut microbiota, IgA transmitted *via* breastfeeding stimulated with the maternal gut microbiota), this may predispose the colonization and selection of specific obesity-associated microorganisms. This microbiota would remain in the gut of the child and would perpetuate an obesogenic-microbiome-associated phenotype in early-life. The child may therefore be “primed” to be colonized by a dysbiotic maternally-transmitted gut microbiota and impairing the immune tolerance profile and overall obesogenic phenotype of the child.

### 3.3. The impact of other early-life factors on obesity

Other studies, while evaluating the potential role of maternal gut microbiota on the offspring gut microbiota, also reflected on the impact of additional factors,



**Figure 3.** Impact of maternal cardiometabolic disease and gut dysbiosis on early-life immunity (created with BioRender).



**Figure 4.** Transmission of maternal gut microbiota and impact on the child's immunity (created with biorender).

such as early-life nutrition and maternal diet, and how they correlated with early-life risk of developing obesity. In fact, as described in the first part of the review, the early-life gut microbiome is influenced by the birth mode, antibiotics, diet, and breast feeding. As such, studies linking obesity and gut microbiota in early-life that do not account for those variables may bias the conclusions obtained, and caution should be taken when analyzing the results. In humans, Tun *et al.* (Tun *et al.* 2018) also verified that, in a cohort of 935 mother-child pairs (aged 1 and 3 years), birth mode and gut microbiota of the infant (Bacillota richness, especially of the *Lachnospiraceae* family) mediated the association between maternal pre-pregnancy overweight and childhood overweight at ages 1 and 3 years, with children born *via* cesarean to overweight mothers being more at risk of developing childhood obesity, compared to infants born to healthy mother and delivered vaginally. However, the genera of *Lachnospiraceae* family differed between infants delivered vaginally and those delivered *via* cesarean birth. Haddad and colleagues focused on the impact of breastmilk exposure and maternal pre-pregnancy BMI in early-life gut microbiota and infant growth measures (BAZ – BMI-for-age z-score; LAZ – Length-for-age z-score; LWZ – Length-for-weight z-score; and WAZ – Weight-for-age z-score) in 33 mother-baby dyads, at 6 and 12 months postpartum. The authors observed that, although maternal BMI was positively correlated with infant anthropometric measures, it was not

associated with gut microbiota composition. The differences in breastmilk exposure were the key drivers in microbial composition differences, with infants who did not receive breastmilk at or after the 6-month timepoint, displaying a profoundly different gut microbiota from infants who continued breastfeeding. Nonetheless, results indicated that increased exposure to maternal breastmilk resulted in decreased microbial richness, possibly due to the selective enrichment of bacterial species associated with HMO degradation. The authors suggest that other external factors, besides maternal BMI, such as diet, host genetics, and lifestyle may also impact early-life microbiota composition and, consequently, the child predisposition to develop diseases (Haddad *et al.*, 2021).

The gut microbiota, can also be impacted by host-related factors, such as geographical location and ethnicity. Despite the fact that variations in gut microbiota composition across distinct ethnicities remains poorly explored, a few studies have started to uncover these differences. Concerning early-life, a recent study by Balakrishnan *et al.* assessed ethnic variability in the gut and oral microbiome of African American and European American children, and its correlation with childhood obesity (Balakrishnan *et al.*, 2021). The authors observed significant differences in gut microbiota diversity (alpha and beta diversity) between both groups, and a prevalence of specific taxa depending on ethnicity (for instance, African American children displayed higher levels of *Ruminococcaceae* and

*Oxalobacter*, which have been associated with obesity) (Balakrishnan *et al.*, 2021). Other studies have found that these ethnicity-dependent differences in gut microbiota composition could be observed in infants as young as 3 months old, before the introduction of more complex diets, and that can persist throughout childhood (Mallott *et al.*, 2023; Xu *et al.* 2020).

Important to note that the gut microbiome is not the only being associated with obesity. Many studies are now also exploring the role of oral microbiome in obesity. The oral microbiota harbors a diverse community of microbes that sustain the homeostasis of the oral cavity (Schamarek *et al.* 2023). The oral-gut axis has been explored not only due to its bidirectional link (since these niches share some taxa), but also for its impact in the development of metabolic pathologies, as recently reviewed (Yamazaki and Kamada 2024 and Schamarek *et al.* 2023)). In early-life, recent research have started to unravel the role of gut and oral in childhood obesity (Wang *et al.* 2023). Ma and colleagues characterized the oral and gut microbiota of a cohort of children, aged 3 to 5 years old, with and without obesity (Ma *et al.*, 2023). The results indicated a significant difference in alpha-diversity between the two groups, with obese children displaying the highest diversity in the oral microbiota, and the lowest in the gut (Ma *et al.*, 2023). Furthermore, oral samples of obese children were enriched in *Filifactor* and *Butyrivibrio*, while fecal samples presented higher abundance of *Faecalibacterium*, *Tyzella* and *Klebsiella*, considered biomarkers for obesity (Ma *et al.*, 2023). Coker and co-authors assessed the relationship of oral microbiota composition and weight gain and found that beta-diversity was inversely correlated with infant BMI and z-scores (Coker *et al.*, 2022). Concerning oral microbiota composition, the authors found certain taxa, namely *Streptococcus mitis* and *Corynebacterium matruchotii*, to be associated with weight gain (Coker *et al.*, 2022). Despite these recent findings, both articles highlighted the need for further research, as the impact of oral microbiota (and its link to gut microbiota) in the development of childhood obesity remains poorly studied. It is also relevant to emphasize the potential role of the maternal oral microbiota, in the establishment of the offspring oral microbiota and health outcomes (Saadaoui *et al.* 2021).

#### 4. Conclusion

The infant gut microbiota has a profound impact on the development and maturation of early-life immunity, by establishing a symbiotic link between the commensal microorganisms of the child and its immune system. In homeostasis, there is a tolerance system

that strictly regulates and prevents an overreactive immune response toward the gut microbiota, allowing the proper development of the immune system of the child. However, disruptions to the gut microbiota during this period have been linked to the development of diseases, such as obesity. Recent studies have highlighted the importance of the mother as the main source of microorganisms to the offspring, particularly in the transmission of dysbiotic gut microbiota and its potential impact on future health. Research conducted to this point seems to support the proposed hypothesis that obesogenic maternal microbiota could lead to the development of obesity in children, namely through the transfer of bacterial species associated with higher BMI that persist and modulate the immune system of the infant, generating an abnormal immune response. Nevertheless, further studies (in comprehensive cohorts of mothers and infants) are necessary to understand the mechanisms associated with the interaction of dysbiotic gut microbiota and childhood obesity, as well as the mechanism that explains the reason why maternal strains are more likely to adapt and remain in the child's gut.

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