The human gut microbiota: a dynamic interplay with the host from birth to senescence settled during childhood

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The microbiota "organ" is the central bioreactor of the gastrointestinal tract, populated by a total of 10^{14} bacteria and characterized by a genomic content (microbiome), which represents more than 100 times the human genome. The microbiota plays an important role in child health by acting as a barrier against pathogens and their invasion with a highly dynamic modality, exerting metabolic multistep functions and stimulating the development of the host immune system, through well-organized *programming*, which influences all of the growth and aging processes. The advent of "omics" technologies (genomics, proteomics, metabolomics), characterized by complex technological platforms and advanced analytical and computational procedures, has opened new avenues to the knowledge of the gut microbiota ecosystem, clarifying some aspects on the establishment of microbial communities that constitute it, their modulation and active interaction with external stimuli as well as food, within the host genetic variability. With a huge interdisciplinary effort and an interface work between basic, translational, and clinical research, microbiologists, specialists in "-omics" disciplines, and clinicians are now clarifying the role of the microbiota in the *programming* process of several gut-related diseases, from the physiological symbiosis to the microbial dysbiosis stage, through an integrated systems biology approach.

ROLE AND FUNCTION OF THE HUMAN MICROBIOTA

Symbiosis and Dysbiosis of Gut Microbiota: A Landmark to Raise Health During Early Life Stages

Human gut microbiota is a complex ecosystem consisting of a total of 10^{14} bacteria. Its genome, which represents more than 100 times the human genome, can be defined microbiome (1). The microbiota commensals play an important role in human health by acting as a barrier against pathogens and their invasion with a highly dynamic modality, exerting metabolic functions and stimulating the development of the immunitary system (IS) (2). The IS consists of innate and adaptive ISs. The innate IS is the sum of physical and chemical blocks, through reactivity of local nonspecific and specific cells recruited to the site of inflammation. The adaptive IS acts as a specific second line, responding to antigen variability and

producing immunological memory (2). Indeed, the intestinal epithelium at the interface between microbiota and lymphoid tissue plays a crucial role in the mucosa immune response (2). The IS ability to coevolve with the microbiota during the perinatal life allows the host and the microbiota to coexist in a relationship of mutual benefit, which consists in dispensing, in a highly coordinated way, specific immune responses toward the biomass of foreign antigens, and in discriminating false alarms triggered by benign antigens (2). The failure to obtain or maintain this complex homeostasis has a negative impact on the intestinal and systemic health (2). Once the balance fails, the "disturbance" causes the disease, triggering an abnormal inflammatory response as it happens, for example, for the *inflammatory bowel diseases* in newborns (2). Specific determinants of variability between host and related environment act directly on the composition and density of the gut microbiota immediately after birth, resulting in the functional efficiency of the newborn intestine (3). The gastrointestinal ecosystem constituting the microbiota can be represented as a "microbial organ" (named superorgan) (4), located in the host organism (superorganism) and characterized by a dynamic interaction with food and host cells (**Figure 1**).

The strong relationship between gut microbiota and metabolism is progressively emerging as a control key in the gut "plant" energetics, defining the role of gut microbiota metabolome, inflammatory response, and genesis of metabolic alterations (5). First, the causal role of gut microbiota in the control of energy homeostasis was indicated by comparing conventional to germ-free (GF) mice fed a high-fat diet (6). While conventional mice gain weight, the GF mice continued to be lean although daily increased food intake (6), suggesting an impaired feeding efficiency. Body weight gain was greater when the GF mice were colonized with the microbiota from obese rather than from a lean mouse, suggesting that a given microbiota is dependent on the host genome (7). It was then shown that obese patients were characterized by an excess of Firmicutes, when compared with lean controls, and the dysbiosis was inverted under caloric restrictions (8). Interestingly, obese mice showed similar intestinal dysbiosis, suggesting a common mice/humans mechanism (9). Burcelin *et al.* (10)
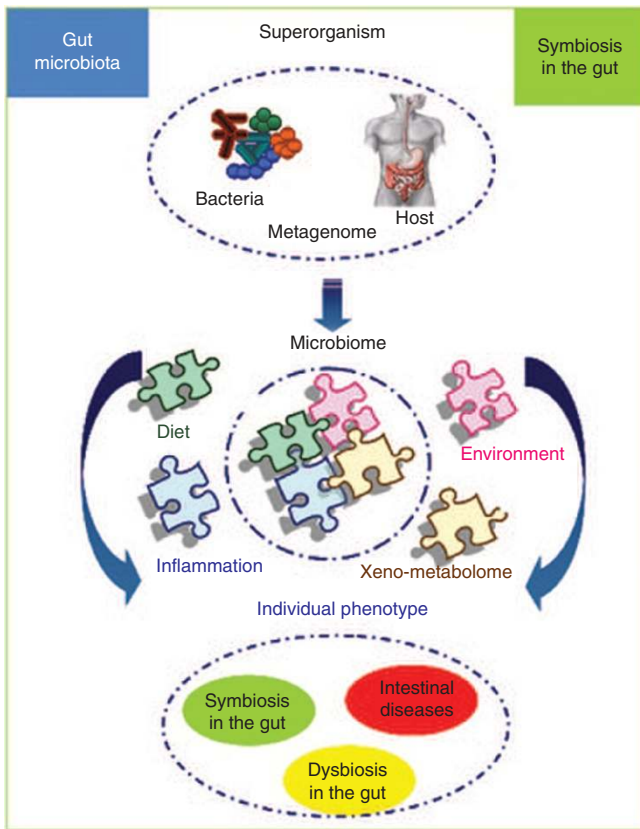
Figure 1. Graphical representation of the superorganism, its interactions with the various variability determinants, and related individual phenotypes. The largest microbiome is located in our gastrointestinal tract, and it is influenced by several external factors, such as diet, inflammation stage, environment, and xeno-metabolome. Each microbiome constitutes an individual phenotype, able to describe symbiosis-, dysbiosis-, and disease-related gut conditions.

showed that C57BL6 mice, fed a high-fat diet, had metabolic phenotypes highly heterogeneous, with different levels of diabetes and obesity, suggesting a metabolic "epigenetic" adaptation unrelated to diet or genotype. Additionally, also antibiotic treatment of obese mice was described as an important dysbiotic effect affecting Firmicutes/Bacteroidetes vs. Proteobacteria ratio (11). Besides hyperglycemia (12), insulin resistance was associated with gut microbiota changes, even in patients with similar body weight, strongly correlating with obesity and type 2 diabetes mellitus (13). The mechanisms can be included in the cross-talk between gut microbiota-inflammasome machinery. Indeed, the nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 and 6 regulate the effector protein interleukin-18, which negatively control liver steatosis, activating bacterial Toll-like receptors (e.g., TLR-4 and TLR-9) (14). Indeed, in a mouse model, Vijay-Kumar *et al.* (15) reported that TLR-5 receptor impairment, involved in the bacterial flagellin recognition, led to a "human metabolic syndrome gut microbiota phenotype," associated with low-grade inflammatory signals. In another study (16), the authors observed a metabolic syndrome after colonization of TLR-2 GF deficient mice, protected from diet-induced insulin

resistance. The TLR-2 deficient mice became resistant to insulin and therefore obese, suggesting a correlation with the increased fat storage or with the augmented levels of gastrointestinal lipopolysaccharide (LPS) permeability and absorption. Recent data have started to characterize the human dysbiosis also during liver disease (17), showing a statistically significant increase of Proteobacteria in pediatric obesity, compared with nonalcoholic steatohepatitis (18). Metabolic diseases are linked with disruption of both innate and adaptive ISs (19). It is now widely accepted that overproduction of some cytokines (e.g., tumor necrosis factor-α and interleukin-1) contributes to insulin resistance thereby promoting diabetes (20), through infiltration into adipose tissue, leading to a tissue metabolic inflammation (21), as well as Gram (−) LPS components (22), which then circulate in the blood through LPS-binding proteins and lipoproteins accumulated during the feeding period (23). In the proximal gut segments, even under homeostasis, where the microbiota is rare, some commensal bacteria can be in close contact with the epithelial cells. The IS scavenges these bacteria and generates primary T-cell responses, either immunogenic or tolerogenic (24). However, this concept, validated in healthy subjects and in patients with inflammatory bowel disease, has to be reconsidered in metabolic diseases, because gut dysbiosis can be induced within a few days or weeks by a diet change (25), allowing pathogens to penetrate the body without being destroyed by the innate and specific adaptive ISs, through a nucleotide-binding oligomerization domain 1- and LPS-cluster of differentiation 14–dependent translocation mechanism, which, when hampered, improves insulin sensitivity (26). Thereby, the blood might not be a direct route for bacterial translocation, suggesting the possibility of a tissue microbiota, also mediating allergy response (27). To identify million of bacterial genes involved in the control of metabolism is a demanding task. This deserves sophisticated computational pathways that may drive in the assignment of diversified bacterial roles: (i) resilient bacteria (acting in "early" inflammation), (ii) responsive bacteria (players in "late" inflammation), and (iii) (e.g., infections, inflammatory bowel diseases *status*) hence translating "roles" into the framework of "*real case sample diversity*" (28). However, to date, case–control studies include only limited numbers of individuals/patients, while *genome-wide* and *metabolic-wide* studies should be necessary to provide predictive disease models especially during infancy and childhood, when rigorous variation indexes are tremendously important to comply with development and growth variables. This computational framework involves sophisticated biostatistical and bioinformatic models to describe gut microbiota genome and metabolome and its cross-talk with the host. This strategy allows the manipulation of very large data sets (metagenomic and metabolomics) to combine and integrate several variables in a one-step procedure to simplify predictive models (29,30) and to evaluate microbial ecosystems in terms of diet impact (therapeutics), extremely important during the first years of life (31,32) (**Figure 2**). Indeed, the thorough description of a gut *healthy* microbiota in the early stages of life plays a crucial role in establishing a good nutritional practice
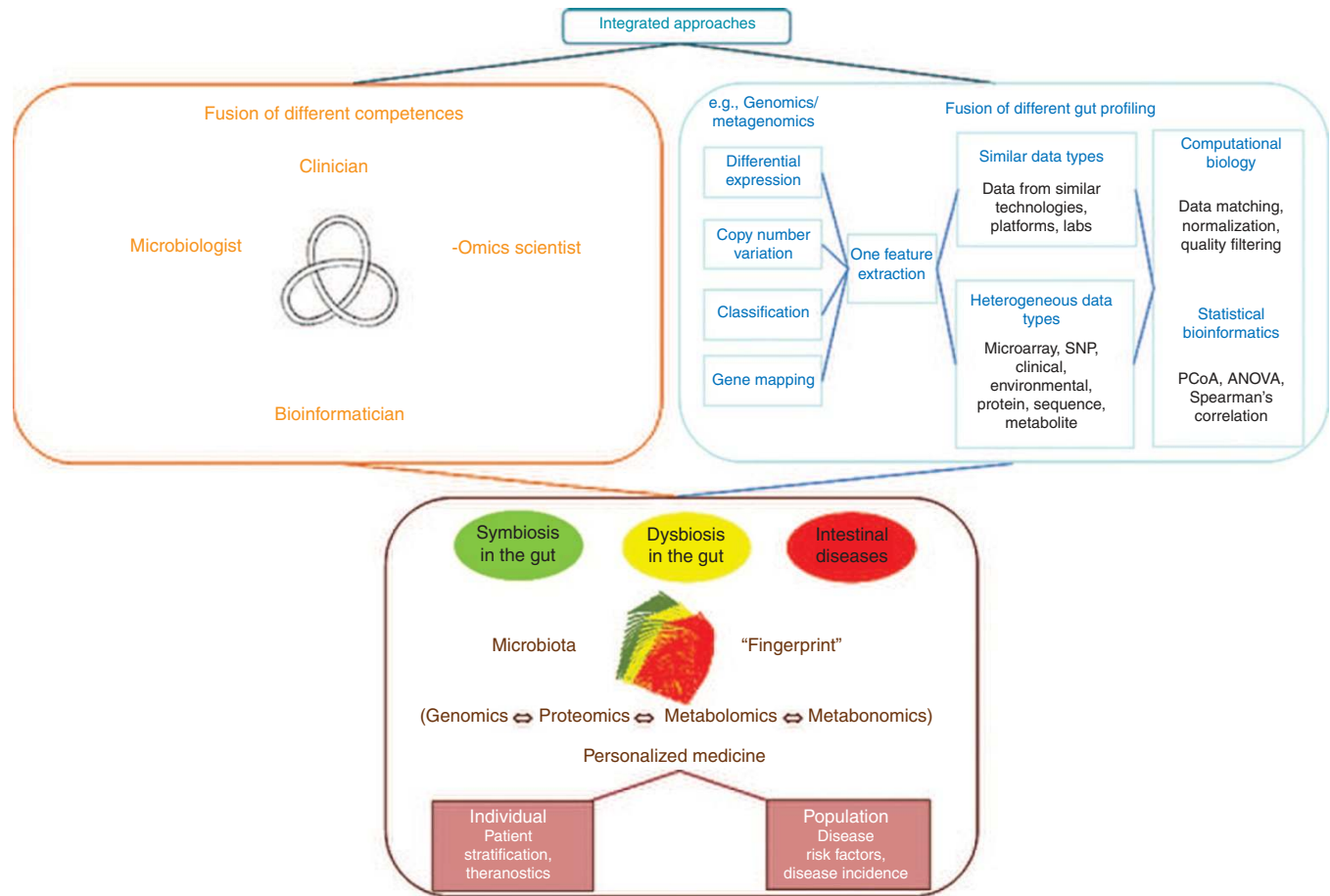
Figure 2. The "knot -omics" strategies and clinical needs: the key to disentangle gut microbiota–related diseases through the symbiosis–dysbiosis route. Chaotropic bacterial factors contribute to the onset of gut symbiosis imbalance, generating entropy, triggering inflammation, and inducing, in some cases, disease status. The different levels of complexity can be unveiled by new "-omics" approaches. Such approaches need heterogeneous multidisciplinary competences, integration of different types and levels of data, and production of specialized and dedicated operational pipelines. The result of such integrated approaches provides "-omics" charts to "fingerprint" gut microbiota in different case controls, hence defining individual- and population-based gut microbiota profiling. PCoA, principal coordinate analysis; SNP, single-nucleotide polymorphism.

in child care and pediatrics, but especially in providing nutraceutical benefits and ensuring a healthy growth and, therefore, a healthy aging (1).

Dysbiosis Progression of Gut Microbiota: A Prediction Tool of Disease Since Childhood

The description of potential dysbiosis "types" in childhood is still lacking and should include rigorous criteria for unbiased recruitment rules, actually reflecting individual multiplicity and development baselines. Indeed, population studies, if properly linked to host physiology traits, can provide an exhaustive understanding of the gut microbiota dysbiosis impact in childhood. At the Bambino Gesù Children's Hospital (OPBG), an epidemiological survey is operative to evaluate dysbiosis impact on different stratified "healthy" children (**Figure 3a**). Indeed dysbiosis is the prelude to a wide range of diseases, such as obesity (11,33), type 2 diabetes (33,34), liver steatosis (18,35), behavior abnormalities (36,37), atopy and allergy (38,39), metabolic disorders (40), inflammatory disorders (14,41), inflammatory bowel diseases (42), including enterocolitis, necrotizing enterocolitis (NEC) (43,44),

or Hirschsprung syndrome, progressively appearing during childhood (**Figure 3b**).

Currently, particularly the onset of obesity has shifted to the early years of life, and the prevalence of pediatric obesity has dramatically increased on a global scale (31). While the epidemic of obesity is mainly attributable to the Western lifestyle with an excessive consumption of carbohydrates and fats, along with reduced physical activity, obesity onset in childhood has been, in part, attributed to the fetus exposure to unfavorable conditions (e.g., nutritional and hormonal dysfunctions) in the uterine life, which can then exert a strong impact on the subsequent development, structure, and function of the child organism (45) (**Figure 3a**). This phenomenon, which extends to perinatal and postnatal age, is known as *disease programming during the development phase* (46). Indeed, it is known that the gut microbiota has an effect on the individual risk to develop diseases in adulthood, especially in case of cardiovascular diseases, as a result of weight gain, fat accumulation, and maintenance of a basic mild inflammation condition (47). In addition, epidemiological studies on human populations have shown some associations between neurological development
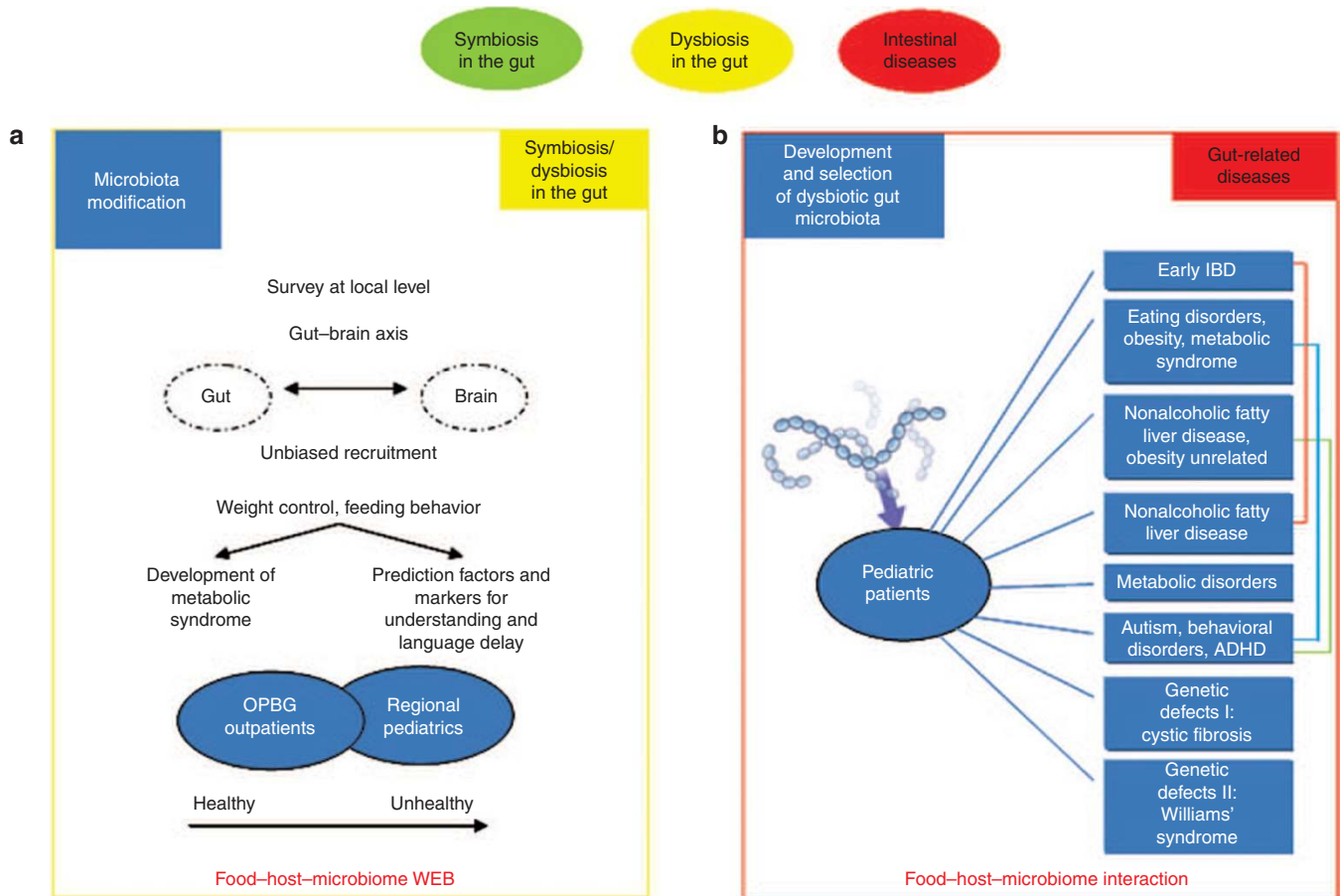
Figure 3. Strategies for dysbiosis controlling at epidemiological level for the major diseases related to the gut microbiota alterations. (**a**) The description of potential dysbiosis "types" in childhood must include rigorous criteria for unbiased recruitment rules, reflecting individual multiplicity and different development baselines. The definition of these types, obtainable by epidemiological surveys, may throw light onto complex physiological networks, such as the gut–brain axis, linking behavioral and food-related endophenotypes to obesity mechanisms. (**b**) The development and selection of dysbiotic gut microbiota can lead to gut-related diseases occurring during infancy and childhood: IBD, eating disorders, obesity, metabolic syndrome, nonalcoholic fatty liver disease, metabolic disorders, autism, behavioral disorders, attention deficit/hyperactivity disorder (ADHD), and genetic defects, such as cystic fibrosis and Williams' syndrome. IBD, inflammatory bowel disease; OPBG, Bambino Gesù Children's Hospital.

disorders, such as autism, schizophrenia, anxiety, and microbial communities' (MCs) composition in the perinatal period (48). These findings were strengthened in the animal model, in particular in GF mice in which it has been shown that exposure to microbial pathogens during early life experiences results in behavior abnormalities, such as anxiety, dissociated cognitive function, and altered motor activity (49). Therefore, in general, mutual relationships within the gut microbiota affect the metabolic "health," regulating energy balance, xeno-metabolome (e.g., metabolism of xenobionts), resistance to pathogen colonization, IS maturation in children, and management of its homeostasis in adults, giving to the gut microbiota the *dignity of organ*.

MOTHER–CHILD SYMBIOSIS

During its uterine life, the fetus develops in a sterile environment. The presence of bacteria in the amniotic fluid, when revealed, causes amniositis, funisitis, and chorioamniositis and, therefore, is often associated with a preterm delivery (50). At birth, the baby's intestine is mostly sterile and soaked in amniotic fluid, but within a few days it is colonized by bacteria

coming mainly from the mother but also from the external environment (51). The formation of the gut microbiota ecosystem is a complex but continuous process, affected by endogenous and exogenous determinants of variability, with an immediate effect at the time of birth that continue for several years during childhood through subsequent stages (52) (**Figure 4**). One of the major causes of onset and modulation of the newborn gut microbiota is the mode of delivery. A pioneering scientific work has described the MCs of the newborn, articulated in different ecological niches, as *non-specialized*, contrary to the *highly* differentiated MCs of the mother. Children born by natural delivery develop MCs similar to their mothers' vaginal microbiota (e.g., *Lactobacillus* spp., *Prevotella* spp., *Sneathia* spp.), while children born by Caesarean section (CS) are characterized by MCs similar to mother skin microbiota (e.g., *Staphylococcus* spp., *Corynebacterium* spp., *Propionibacterium* spp.). The vaginal MC is characterized by relatively few bacterial species, with Lactobacilli constituting the 50% of the whole microbial ecosystem, also during birth, even in a geographic-dependent manner (53). On the contrary, babies born by CS, present MCs not necessarily mother induced, but often reflecting skin ecosystems of
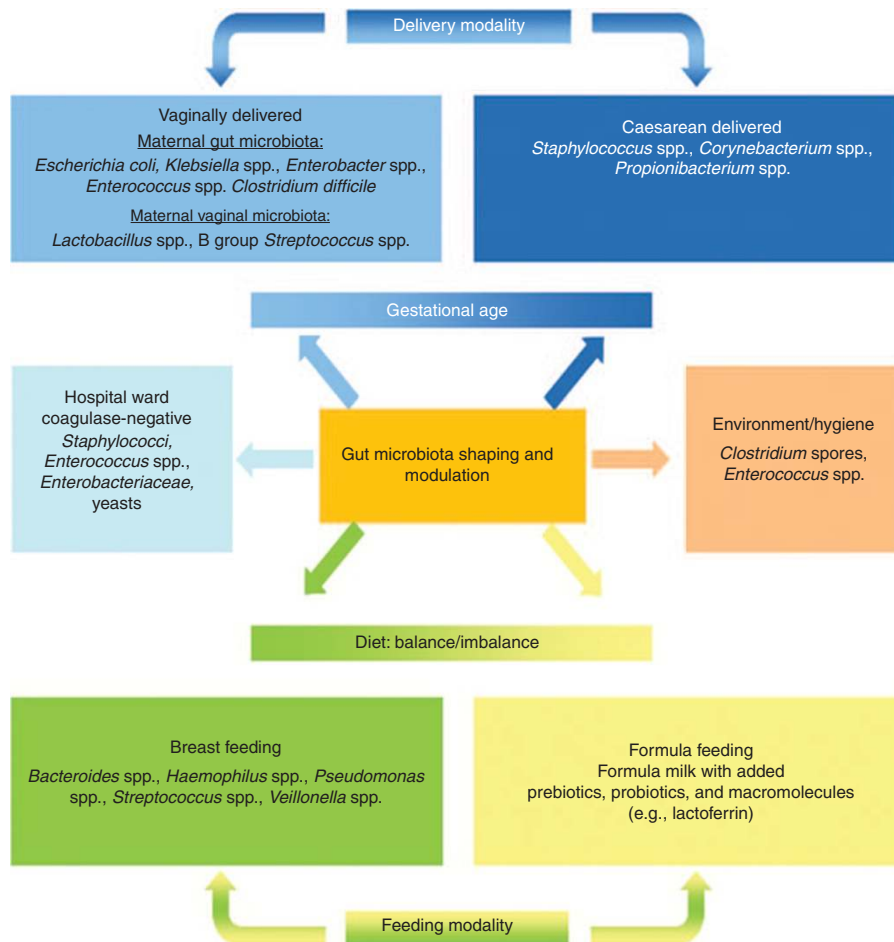
Figure 4. Illustration of the main determinants of variability affecting the gut microbiota ecosystem. During early life, several external factors, such as delivery mode, feeding modality, environmental influences, antibiotic exposure, and functional food intake, can affect microbiota shaping and composition. Vaginally born babies acquire bacterial communities that resemble their mother's vaginal microbiota, while Caesarean delivered babies harbor bacterial communities that are similar to the skin surface communities of the mothers. Additionally, breast-fed newborns show a more uniform and stable bacteria population compared with formula-fed newborns. Moreover, the environment during delivery, antibiotic treatment, and hygiene measures can influence the composition of the gut microbiota in neonates. Finally, the intake of functional foods, containing probiotic, prebiotic, or bioactive proteins (e.g., lactoferrin), modify the gut microbiota, reducing pathogen growth.

healthcare workers, surfaces, surgical means, etc., which may come into contact with the baby during delivery. Therefore, in this case, the interaction with the environment causes to the newborn the acquisition of microbial ecosystems with more marked "environmental" ecologies. The delivery mode influence persists for months and, perhaps longer, after the birth (54). This could be at the basis for an increased susceptibility to pathogens, such as methicillin-resistant *Staphylococcus aureus*, present in 64–82% of CS-born infants (55). This initial "bacterial imprinting" may later on differentially contribute to the onset of atopic diseases, allergies, and asthma, described as more frequent in CS-born children rather than in those naturally delivered (56). It might be interesting to consider that the vaginal Lactobacilli are bacteria occupying *from the beginning* (pioneers) specific sites in the niche of the newborn gut microbiota, establishing a defensive role against the pathogens but also creating maximum compatibility with the subsequent intake of Lactobacilli because of feeding (57). The presence of Lactobacilli in the vaginal microbiota may modulate the symbiotic mother–child interaction (2) and is indicative of maternal

metabolic abnormalities, such as the high birth weight (e.g., excessive weight gain in pregnancy or altered glucose metabolism) (57). In fact, many of the metabolic and immunological changes during pregnancy are the same as those describing the metabolic syndrome. A recent study on pregnant women showed the transferability of the metabolic syndrome symptoms to their infants, studying varying pre-pregnancy body mass index and gestational diabetes (58). Microbiota of pregnant women changed dramatically between the first (T1) and the third (T3) quarters, showing an increase of interindividual diversity (enterotypes). In particular, the authors observed in T3 an increase of Proteobacteria and Actinobacteria, but an overall decrease of the Operational Taxonomic Units multiplicity. Moreover, they reported in T3 the highest amount of inflammation markers and the increase of energy extraction efficiency, although the *repertoire* of the host gene transcription remained constant throughout the entire gestational quarters. The T3 microbiota transferred to GF mice induced insensitivity to insulin and a higher adiposity when compared with the one from T1. These data suggest that the microbiota–host

interactions have a great impact on the mother metabolism, especially in the later highly energy-requiring lactation. However, regarding the correlation with the descendants, the study by Koren *et al.* (58) showed that the newborn microbiota was much more similar to T1 microbiota rather than T3, thus suggesting a selective disadvantage in transferring to the infant the T3 Operational Taxonomic Units. However, the observation that a human microbiota induces a *gestational* metabolism in GF mice disagrees with another recent work that demonstrates how an exogenous colonizing microbiota should be species specific (59). In pregnant, overweight women, a decrease of Bifidobacteria and Bacteroides and an increase of Staphylococci and Enterobacteriaceae (especially *Escherichia coli*) compared with those of normal weight pregnant women have been reported (60). Other authors have correlated the composition of the newborn gut microbiota to the mothers' weight but found increases in Clostridia, *Bacteroides*, Staphylococci, and *Akkermansia* species during pregnancy (61). The increase of Enterobacteriaceae in pregnant women was also functionally related to an increase of ferritin and a reduction of transferrin, while the quantities of *Bacteroides* were associated with increased levels of high-density lipoprotein (HDL) cholesterol and folic acid (60). In animal models, pregnant and obese mice females showed a reduction of 50% of *Bacteroides* and a proportional increase of Firmicutes, compared with normal mice submitted to the same diet (8); such alteration might cause the excessive energy storage (8). The antibiotic treatment before or during the CS delivery (62) is another cause of unborn microbial ecosystem modulation, with a direct effect on the relative Gram (+)/Gram (−) abundances (2). Other variability factors can be the hygiene precautions taken during delivery, as well the newborn degree of prematurity (2) (**Figure 5**). Even the breast milk may represent an abundant inoculum of bacteria, while in solid food bacteria such as *E. coli* or, in general, Enterobacteriaceae and, as already mentioned, Lactobacilli, have not been frequently found (63). During lactation, in fact, the cells of the intestinal lymphoid tissue travel to the breast through the lymphatic system and the peripheral blood, thus facilitating the transfer of both the intestinal and the mammary skin microbiota to the breast-fed newborn (63).

It is known that oligosaccharides, glycoconjugates, and natural components of human milk may prevent the attack of enteropathogens and stimulate Bifidobacteria growth (64). Other constituents of human milk, such as interleukin-10, epidermal growth factor, transforming growth factor-β1, and erythropoietin, can represent important mediators in the inflammatory response. Pups of mice colonized with *S. aureus* and *E. coli* have shown an increased incidence and severity of NEC, if compared with intestines containing multiple bacterial species (65).

After delivery, breastfeeding continues to improve the original inoculation of Lactobacilli and Bifidobacteria and of bacteria from the mother's skin, thus making the child's microbiota particularly rich in Bifidobacteria (61).

The microbiota structure can also be altered by an exposure to probiotics, when breastfeeding is not possible (66); additionally,

such an effect may also be related to a prolonged reduction of allergies in CS-delivered children (67). Maternal and newborn treatments are another determinant of variability. Babies born to mothers treated with antibiotics in the perinatal period seem to have a lower quantity of *Bacteroides* (e.g., *Bacteroides fragilis*) and of *Atopobium* cluster members (54). Rougé *et al.* (68) have shown that the gastrointestinal of preterm babies born at less than 33 wk of pregnancy has a low biodiversity.

FROM BIRTH INTO ADULTHOOD

The problem of how the bacterial inoculum at birth later differentiates in the various microbial ecosystems in several human districts and what are the different associated ecologies are now a topic of great interest and discussion in the scientific community (**Figure 6**). The first step in understanding this aspect is surely to know what are the reference species "founders" of the microbiota in the infant at birth, from which later the subsequent Operational Taxonomic Units derive. This evolution can be interpreted using the tools of *the ecological theory of succession*, developed by plant ecologists (69). Little is known about the time-dependent mechanisms of the human microbial ecosystems development from the founder communities at the very early life stages (70–72). As previously mentioned,
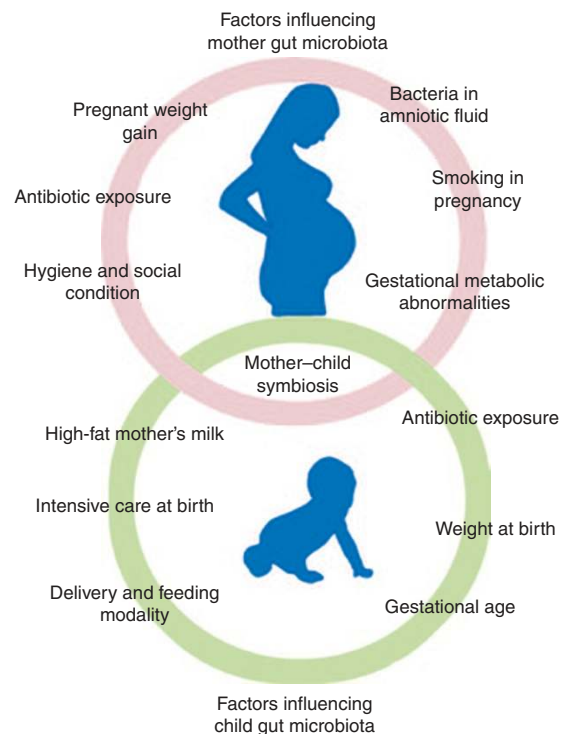

Figure 5. Mother–child symbiosis elements affecting the onset and modulation of the newborn gut microbiota. Based on the complex mother–child symbiosis, a plethora of factors affecting child gut microbiota actually resides in maternal physiology, hence preparing a "dynamic" baseline for the following interventions of external stimuli on newborn gut microbiota. An incorrect maternal behavior (e.g., smoking and weight gain in pregnancy), poor social condition, and diseases during pregnancy can negatively influence the newborn gut microbiota composition. Furthermore, environmental factors, such as delivery and feeding modality, can significantly drive the newborn gut microbiota.
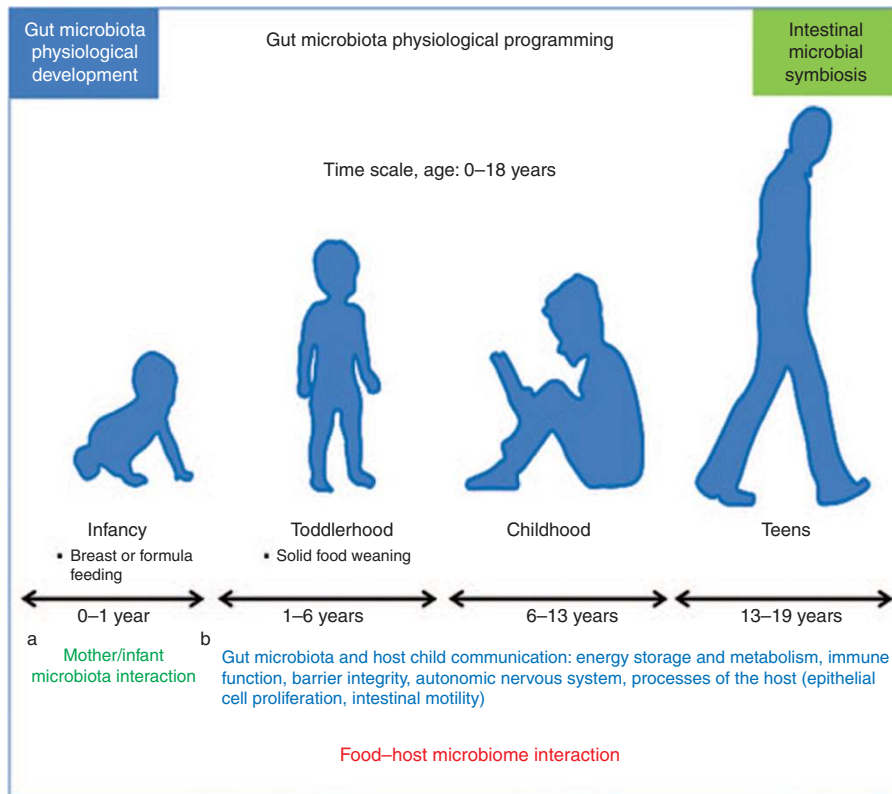
Figure 6. Physiological conditions of the gut microbiota during age of development from birth to adulthood. In the pediatric age scale, 0–18 y has been divided for convenience into 4 main groups, representing a scheme of child development stages in which birth, feeding, and environmental, social, biological, and genetic factors progressively influence the entire individual psychosomatic development, intimately connected to the gut microbiota onset and modulation. During infancy, external factors, such as delivery mode and feeding modality (breast or formula feeding), in the context of the mother/infant axis, electively and massively exert the first substantial action on the gut microbiota onset and further modulation. During toddlerhood, the intake of solid food and the maturation of immune system profoundly modify the gut microbiota profiles toward adult gut microbiota setting. During childhood and in teens, the maturation of hormonal and sexual development, social behavior, and adult-like diet and lifestyle changes continue to affect, but to a lesser extent, the gut microbiota shaping. Scheme of age scale 0–18 y and physiological programming and gut microbiota: (**a**), from 0 to 1 y infant gut interacts with mother; (**b**), from 1 to 19 y, child gut microbiota plays a crucial role in energy storage and metabolism, immune function, barrier integrity, autonomic nervous system development, epithelial cell proliferation, and intestinal motility.

children born by natural delivery at birth show a gut microbiota reflecting the mother's vaginal microbiota, as detected in meconium samples (51,53,73). Therefore, the first microbial acquisition seems to be governed by a vertical transmission from mother to child and only later develops into differential MCs associated with various anatomical districts (74). However, the definitive influence of the host genotype on the microbiota remains questionable. Indeed, in a further study carried out in 2009 on 31 pairs of monozygotic twins and 23 pairs of dizygotic twins, Turnbaugh *et al.* (75) reported that the microbiota of monozygotic twins was not significantly more similar than that of the dizygotic twins. Therefore, no study so far has provided a genetic demonstration of the heritability of the gastrointestinal human microbiome. One possible reason for these conflicting results is that studies carried out on twins have compared entire communities, perhaps underestimating the dynamics of the familiar subsets in the whole community. While the strain pioneers of contamination at time zero (delivery) derive from the mother's skin, vaginal, or gut ecosystems, the subsequent ones are of uncertain origin (76). The strain diversity increases rapidly during the first years of life, although with a considerable

degree of instability (70,71). However, the reason for this diversity increase is not known: it might be that new bacteria are incorporated at a constant speed in the microbiota ecosystem in a way dependent on how they have lived in the environmental ecosystem or that they need to grow in such a complex system of more differentiated and distinct niches, or that they originate a habitat larger than the individual niches (77). Biogeography studies have shown that large islands support multiple species and that the increase of the functional complexity produces *per se* a taxonomic complexity, until the attainment of the equilibrium state, characterized by an "adult" microbiota type (mainly formed by Firmicutes and Bacteroidetes) consisting of a complete *suite* of functions, at approximately one and a half years of age (71). Although comparisons between individual children show great differences in the dynamics of colonization, in a single child, consortia of bacterial taxa are not casual at any given time, thus indicating that microbes depend on each other for the consortium constitution (70). This microbial plasticity may constitute an adaptive modality, selectively favorable to the highly variable changing of the gut physiological development in childhood. It is unclear how the geographical location,

life style and conditions, puberty, illness, and other factors may affect the microbiota stability in the course of each individual's life (78,79). The process of bacterial succession in early childhood that varies from individual to individual (80), as already mentioned, can be a model for understanding the process of adults recolonization after antibiotic therapy.

CONCLUSIONS AND FUTURE PERSPECTIVES

Feeding in the first months and years of life is one of the most important determinants of children's health, affecting the IS future actions and even the healthy status in adulthood. The gut microbiota development may be closely related to the allergic sensitization in early childhood, and predispose to metabolic imbalances underlying obesity and cardiovascular risk in adulthood. Understanding the dynamics of bacterial populations and treating them, rather than fighting them with antibiotics, may be in the future the winning strategy to eradicate many diseases and the increasing phenomena of antimicrobial resistances. Therefore, it would be possible to manage the MCs on the basis of their content and metabolic balance, exploiting systems biology strategies. The classical concept of infection associated with a single organism that invades our body and reproduces causing a series of alterations is no longer correctly applicable. The higher the difference among bacteria, the smaller the chance that external pathogens can invade us and settle in internal niches of the human body. In fact, if all the districts are occupied, it becomes difficult for the "invaders" to find a place and become operative. In fact, it has been found that some diseases seem to be caused by imbalances in those organisms that *communicate* with the host. This new model can be extended to various diseases and not only limited to infectious processes. However, the microbiota role is not only in the "exclusive competition" in the pathogenesis: our microbiome interacts with the environment at the side of our *multigenetic set*. Actually, we would have two genomes: the human genome and the microbiome, and therefore, the *fluctuations* in the genome that constitutes the microbiota would translate in the manifestation of dysbiosis and, then, in the subsequent onset of diseases (or in their remission). The interdisciplinary work of microbiologists and "-omics" scientists, run at the interface between research and clinics, is getting light onto the role of the gut microbiota under physiological and pathological conditions, assigning it some genetic and phenotypic features (*fingerprints*) able to define human "enterotypes," especially in infancy and childhood. The ability to describe them and to control their fluctuations will constitute the active passage from the systems biology of the human MCs to the individual systems medicine of the next future.

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