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MODERN DATA ON THE INTESTINAL MICROBIOME AND THE STAGES OF ITS FORMATION

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Abstract. The human microbiome is a collection of microorganisms, mainly bacteria, that inhabit the human body. In today's world, the relationship of a macroorganism with intestinal microbes is the result of evolution over a lifetime of thousands of generations. In recent years, due to metagenomic analysis, about 240 new species of microorganisms of the gastrointestinal tract have been isolated and described, many of which have not yet been cultivated. In the process of evolution, microorganisms adapt to environmental conditions and acquire an increased ability to reproduce. Despite the use of genomic technologies, the issue of microbial colonization of the fetus remains debatable. It has been established that the microbiome (odontogenic, intestinal, vaginal) of the mother and the sanitary state of the environment determine the nature of the primary colonization of the child. Subsequently, the composition of its intestinal microbiota largely depends on the nature of feeding. The human milk microbiome is quite complex, dynamic and changeable throughout lactation. The gut microbiota of a breastfed infant is characterized by a high population level of infant bifidobacteria species (90%) and a low content of *C. difficile* and *E. coli*. The introduction of complementary foods modifies the bacterial diversity in the baby's intestines. It is shown that the composition of the intestinal microbiota of the child is significantly influenced by the place of residence and visits to the children's institution. Thus, the formation of the intestinal microbiome is a long, complex multifactorial process, the violation of which is associated with the development of various pathological conditions in the child's body. Understanding the mechanisms of microbiome development will allow developing effective methods for the prevention and correction of microecological disorders in a child and related diseases in different periods of life.

Key words: *microbiome; fetus; meconium; intestines; breast milk; infant*

СОВРЕМЕННЫЕ ДАННЫЕ О КИШЕЧНОМ МИКРОБИОМЕ И ЭТАПЫ ЕГО ФОРМИРОВАНИЯ

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Резюме. Микробиом человека — совокупность микроорганизмов, преимущественно бактерий, населяющих его организм. В современном мире отношения макроорганизма с кишечными микробами — результат эволюции на протяжении жизни тысячи поколений. За последние годы благодаря метагеномному анализу выделено и описано около 240 новых видов микроорганизмов желудочно-кишечного тракта, многие из которых еще не культивированы. В процессе эволюции микроорганизмы адаптируются к условиям окружающей среды и приобретают повышенную способность к размножению. Несмотря на

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использование геномных технологий, вопрос о микробной колонизации плода остается дискуссионным. Установлено, что микробиом (одонтогенный, кишечный, влагалищный) матери и санитарное состояние окружающей среды определяют характер первичной колонизации ребенка. В последующем состав его кишечной микробиоты во многом зависит от характера вскармливания. Микробиом грудного молока довольно сложен, динамичен и переменчив на протяжении лактации. Кишечная микробиота ребенка, получающего грудное молоко, характеризуется высоким популяционным уровнем младенческих видов бифидобактерий (90%) и низким содержанием *C. difficile* и *E. coli.* Введение продуктов прикорма модифицирует бактериальное разнообразие в кишечнике малыша. Показано, что на состав кишечной микробиоты ребенка значительное влияние оказывает место проживания и посещение детского учреждения. Таким образом, формирование кишечного микробиома является длительным, сложным мультифакторным процессом, нарушение которого ассоциируется с развитием различных патологических состояний в детском организме. Понимание механизмов развития микробиома позволит разработать эффективные методы профилактики и коррекции микроэкологических нарушений у ребенка и связанных с ними заболеваний в разные периоды жизни.

Ключевые слова: *микробиом; плод; меконий; кишечник; грудное молоко; младенец*

INTRODUCTION

One of the most important scientific discoveries made in the first decade of the 21st century is the revelation of the human microbiome (microbial community), that is, the combination of microorganisms (mainly bacteria) inhabiting the human body. For this reason, the frequently used phrase "human microflora" is not quite correct given the current knowledge. It has been proved that our organism is not just a set of microorganisms, but a real biome — microbiome. The microbiome is in a complex equilibrium with the macroorganism, and their synergistic interactions remain an object of intensive research.

In the modern world, the relationship between the macroorganism and gut microbes is the result of evolution over thousands of generations. For millions of years, evolution has acted both on our 23,000 genes, and on nearly 4 million genes (both human and microbial) that are present both in and on our bodies [1].

Advances in genomic approaches, including phylogenetic marker-based microbiome profiling and shotgun metagenomics have made it possible to describe the composition of the microbiota during phylogeny and the numerous associations between its composition and disease [2, 3]. Shotgun metagenomics is a technique used to sequence many cultured microorganisms and the human genome by randomly cutting DNA, sequencing multiple short sequences, and reconstructing them into a coherent sequence.

Metagenomics provides access to characterize the microbiota at the taxonomic level and at the level of putative functions encoded by numerous microbial genes, but unfortunately it does not provide precise phylogenetic information.

In the last decade, about 240 new species of gastrointestinal (GI) microorganisms have been discovered and described through metagenomic analysis, many of them not yet cultured. Integration with culturing approaches is needed to fully understand the function of the intestinal ecosystem in relation to health and disease.

Systems biology allows us to consider functional analysis of the microbial community, i.e. to perform quantification of metabolic activity through the measurement of RNA by metatranscriptomics [4], proteins by metaproteomics [5] and metabolites by metabolomics. The use of these methods is essential to better understand the molecular mechanisms involved in both symbiosis and dysbiosis.

EVOLUTIONARY PATHWAY OF THE MICROBIOTA

Increasing evidence suggests that shared evolutionary history influences both the microorganism and the surrounding and internal microcosm.

Bacteria originated about 3.8 billion years ago, and the eukaryote lineage, which includes humans, evolved after the oxygenation of the Earth's atmosphere, 2.2–2.4 billion years ago [6, 7]. For a long time, bacteria together with archaea, protists (unicellular organisms belonging to eukaryotic cells) and fungi remained free-living single cells, although some became host-associated, i.e. acquired interspecific forms of coexistence (parasitism, mutualism, commensalism, neutralism, etc.).

In the process of natural selection, microorganisms adapt to environmental conditions and acquire increased adaptability — the ability to reproduce.

The phylogeny of homo sapiens was accompanied by repeated changes in the environment and the nature of nutrition — the main factors of selective pressure (reproductive success), leading to

the reforming of its genome. A prime example is the impact of starvation. The human genome contains adaptive markers that ensure survival under starvation, but the accommodations of the human microbiome that offer energy-saving traits for the human host remain unknown [8, 9].

Along with microbiome representatives, the host immune system evolved to regulate and prevent microbial contamination of tissues, organs and body systems. In the course of evolution, the host immune system, in parallel with its microbiome, has developed sophisticated mechanisms to identify and destroy invading microbes, whether they are microbiome representatives or primary pathogens invading forbidden territories [10].

Environmental reorganization and urbanization lead to maladaptation of the microbiome and immune response, negatively affecting health and causing dangerous diseases.

DIVERSITY OF THE HUMAN MICROBIOME

The microbiome in our body is distributed inhomogeneously. According to its topography and species composition it is possible to distinguish: the microbiome of the skin, oral cavity, respiratory tract, urogenital tract and intestine — the largest microbiome of our body. Each millimeter of the colon is colonized by approximately 1011 microbial cells compared to 108 cells in the small intestine [11].

Currently, more than 1000 species of intestinal bacteria have been characterized. Culture-dependent and independent methods estimate that between 150 and 400 microbial species reside in the intestine of each individual [12]. Most of these species belong to *Bacteroidetes* types (genera *Bacteroides* and *Prevotella*), *Firmicutes* (genera *Lactobacillus, Clostridium, Eubacterium* and *Ruminococcus*), *Actinobacteria* (genera *Bifidobacterium* and *Colinsella*) and Proteobacteria (Enterobacter spp.). The relative proportions of each of these taxa vary dramatically not only between individuals, but even within a single individual throughout his lifetime (Fig. 1) [12–16].

Besides the major types such as *Actinobacteria, Bacteroidetes, Firmicutes*, and *Proteobacteria*, the adult intestinal metabolome encompasses members of less diverse bacterial types, including *Verrucomicrobia, Lentisphaerae, Synergistetes, Planctomycetes, Tenericutes,* and *Deinococcus-Thermus*. In addition to these established phylogenetic groups, SSU rRNA gene sequences of uncultured bacteria can be detected. They cluster within the candidate types TM7, *Melainabacteria* and *Gemmatimonacetes*.

Although each individual's microbiome is unique, studies of taxonomic units and microbiomes in different countries have revealed several common microbial communities [2, 13].

At the same time, the composition of Western microbiomes differed from non-Western microbiomes in a number of parameters [17–26]. First of all, the first ones have 15–30% less microbial species than the second ones [18, 22, 23]. Furthermore,

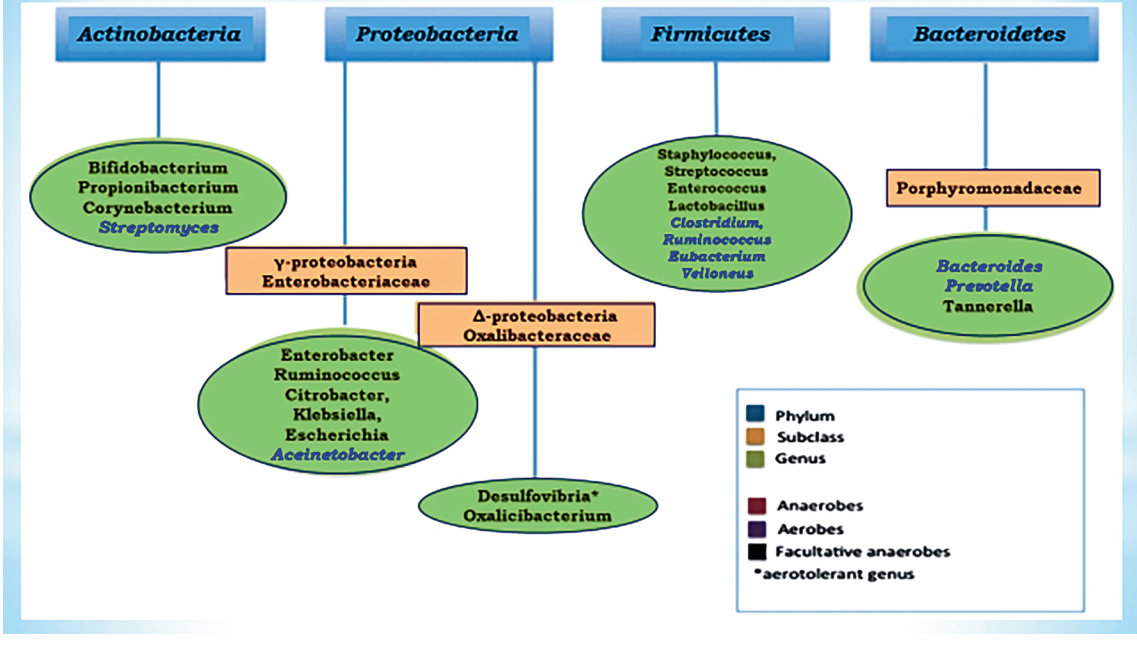

Fig. 1. Major taxonomic units of the human intestinal microbiome

Рис. 1. Крупнейшие таксономические единицы кишечного микробиома человека

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western microbiomes lack certain species that are consistently found in non-western samples. For instance, spiral bacteria of the genus *Treponema*, which appear in the feces of numerous non-Western populations that use raw and wild foods (hunting, fishing, mushroom and berry picking, etc.) [17, 19, 23]. The relative abundance of common types also differs between western and non-western microbiomes. Western ones tend to contain more Bacteroides, whereas non-Western ones contain *Firmicutes* and *Proteobacteria* [19, 21], although there are exceptions to this trend [17].

Thus, studies point to the fact that there is no single "human microbiome" but rather a wide range of configurations that our commensal microbiomes take on.

The existence of these differences in human populations is attributed to diversity in culture, habitat, level of urbanization, hygiene, medicine, lifestyle and diet.

It has been observed that the shift in human diet toward meat-eating over evolutionary time scales is accompanied by a transformation of the intestinal microbial communities [27, 28]. At the same time, increasing fiber and reducing sugar, fat, and meat, a non-Western diet, promotes gut bacterial enrichment [17, 29–31]. Some of the same genes and signaling pathways that differ in quantity between herbivore and carnivore microbiomes also shift rapidly in humans who switch from a vegetarian to an omnivorous diet [30].

One of the hypotheses for the decline in species diversity of the microbiome states that technological and cultural changes accompanying industrialization lead to a "vanishing microbiome" [32]. In addition, living in urban environments, contact with animals, overuse of antibiotics at an early age [32–34], all sorts of intestinal parasites in Western populations [24, 35, 36], and physiological variations such as human-specific loss of N-glycolylneuraminic acid (Neu5Gc) make some contributions.

Alternatively, parts of the microbiome may simply diverge along with human populations as the latter move around the world. For example, the current distribution of *Helicobacter pylori* strains coincides with known human migrations [14, 37].

DEVELOPMENT OF THE GUT MICROBIOME IN ONTOGENESIS

The results of metagenomic studies of the genetic composition and metabolic profile of the intestinal microbiota indicate that this microbiome represents a separate extracorporeal organ of the human body [38]. Like any system (organ) of the organism, the gut microbiome undergoes certain stages of development and maturation.

Intestinal colonization in healthy children fits into four consecutive temporal phases:

- The first lasts from birth to two weeks;
- the second begins after two weeks and lasts until the introduction of the first complementary food;
- The third phase lasts from the introduction of the first complementary food until the end of breastfeeding;
- the fourth — after the cessation of breastfeeding.

From the modern point of view, it is still more correct to distinguish five time intervals, including the antenatal period, and if we consider the entire life course of an individual, then six, taking into account the elderly and old age.

According to many scientists, the intrauterine and neonatal periods are critical stages in the formation of the child's microbiome, which largely determines the state of his or her health throughout life [39, 40].

FROM FERTILIZATION TO BIRTH

Until recently, it was believed that the fetus in the womb is completely shielded from contact with the microcosm, meaning that its antenatal development takes place in an aseptic environment, and the contamination process is established at birth.

A scientific search uses a combination of technologies, namely bacterial DNA sequencing, fluorescence *in situ* hybridization (FISH) method and bacterial culturing in order to determine the presence and viability of the fetal microbiome. It indicates that microbial colonization begins long before birth and is directly dependent on the microecology of the mother [41]. Bacteria of the genera *Enterococcus, Escherichia, Leuconostoc, Lactococcus* and *Streptococcus* are present in the placenta, amniotic fluid, cord blood and meconium [42–52]. Spanish researchers found DNA from bacteria of the genera *Lactobacillus* and *Escherichia coli* in primary stool samples of 20 newborns [43].

In 2014, researchers in Houston, Texas, identified genetic sequences of bacteria from the placentas of 320 women. Biological material was collected immediately after delivery from the germinal part of the placenta (chorionic villi), i.e. the selected samples were not in contact with the microbiota of the birth canal. A wide range of microorganisms were identified in the tissues examined, indicating the existence of a unique placental microbiome. This suggests that the first encounters

with microbes in the infant occur prenatally, even in healthy pregnancies, and are of great importance for both fetal development and the subsequent establishment of the child's microbial system [47].

One study obtained evidence of intrauterine penetration of bacteria from the gut of the mother to the fetus [51]. The researchers assumed that this occurs via the bloodstream and/or lymphatics, a mechanism similar to the "gut-breast axis". This hypothesis is supported by the data of another experiment in which pregnant mice orally received labeled *Enterococcus faecium*, after which these bacteria were detected in the placenta and even in the meconium of unborn mice [51].

A study led by C. Patrick (2019), involved a comprehensive selection of clinical (mother-child) and experimental (female mouse-calf) biomaterial, visualization of the embryonic microbiota in mice, demonstration of dynamic changes in the microbiota during pregnancy in both maternal and fetal (embryonic) sites, and evaluation of the viability of cultured components. Data from the mouse model clearly show that the mouse fetus is exposed to viable and culturable bacteria only in mid-pregnancy, despite positive sequencing results that demonstrate the presence of microorganisms at the end of pregnancy. The authors hypothesized that changes in immune regulation at the level of the utero-fetal barrier may modulate the ability of microorganisms to penetrate and remain viable in the fetal environment.

Clinical results are less clear-cut because the low bacterial biomass of the intrauterine environment (amniotic sac with fetus and germinal part of the placenta) makes it difficult to isolate "contaminants" (bacteria) that may be introduced during sample collection and preparation. However, bacterial signatures that could not be attributed to laboratory contamination were identified in placentas retrieved during cesarean section surgery using NGS sequencing of total DNA banks. These taxa included *Lactobacillus* DNA. In addition, sequencing and culturing results identified common microbial signatures in individual mother-child dyads and discrepancies between fetal/intrauterine samples and controls. Tracing the source of microbial translocation in both a mouse model and in humans found that the placenta represents the matrix (meaning reservoir) of the microbiota [53].

Despite the vast amount of experimental studies, antenatal colonization of the infant remains an area of intense study and debate [54].

Recent developments in a large cohort of women have shown that the majority of bacterial DNA sequences identified in the terminal villi of the human placenta can be attributed to contamination of the internal environment [55].

In June 2021, K.M. Kennedy et al. concluded with a high degree of evidence that fetal meconium samples do not have a "microbial signal.

The researchers established that intestinal colonization in healthy preterm infants does not occur before birth, and the presence of microbial profiles in neonatal meconium reflects populations acquired during and after birth [56].

The concept of sterile fetal development also remains relevant since the current level of knowledge about the mechanisms and functions of transplacental transfer of free nucleic acids is insufficient.

It is well known that the gut and vaginal microbiome changes during pregnancy, but it is still unknown whether these changes have adaptive significance for the mother and/or child.

Due to changes in vaginal pH during pregnancy, bacterial diversity decreases but stability of the microbiota composition increases. Generally, during this period, the vaginal microbiome is dominated by *Lactobacillus crispatus* and *Lactobacillus iners*. The quantitative predominance of these species emphasizes their importance in carrying a healthy baby and maintaining a healthy birth canal environment. It is believed that an altered maternal microbiome allows the fetus to obtain energy from mother's blood more efficiently or that butyrate-producing bacteria may support intestinal epithelial function and contribute to immune tolerance and nurturing of the unborn child [57–59].

An unfavorable variant of vaginal dysbiosis in pregnant women is a decrease in *Lactobacillus* spp., an increase in *Gardnerella* and *Ureaplasma* spp. and, definitely, a colonization of *Candida albicans*. *Burkholderia, Streptosporangium* and *Anaeromyxobacter bacteria* were found in the placenta of women with preterm labor, while *Paenibacillus* predominated in mature infants [60].

Thus, the type and number of bacteria in the different microbiocenoses and amniotic fluid of the expectant mother are important for the outcome of pregnancy and the birth of a healthy infant.

WHAT WE KNOW

Fertilization takes place in an immune-protected organ, the uterus. In turn, immune protection means lack of colonization, but not infertility specifically. It is possible that some bacterial cells from the cervix [108] penetrate with the sperm during fertilization and reach the egg, accompanying the

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implantation process and the period of early embryonic development. Despite this fact, immunity seems to prevent the establishment of a microbial community in "protected" organs. The uterus, placenta, fetus, and blood appear to be free from microbiota, although they may contain bacterial DNA or even some isolated live bacteria [9].

There is an ongoing debate whether the presence of bacterial DNA contradicts the concept of sterility. It has been shown that the presence of circulating bacterial DNA in the blood or placenta, or even the sporadic finding of live transient bacteria, does not indicate infection and does not challenge the current paradigm of immune-mediated organ sterility [47, 61]. Of course, transient "minisepsis" can occur when live microbial cells enter the blood after trauma, microtrauma, or "leakage" of mucous membranes (rupture of fetal membranes or formation of microscopic fissures in them) [62]. In addition, transient bacteremia due to tooth brushing in individuals with periodontal disease is possible [63]. Foreign elements will undergo elimination by phagocytic cells in healthy individuals with an adequate immune response sooner than colonization and assembly of microbial communities occurs. Otherwise, if it concerns a future mother, a complicated course of pregnancy is possible.

K. Aagaard et al. (2014) compared the taxonomic profile of the microbiome of the placenta and various microbiocenoses (intestine, oral cavity, skin, genitourinary tract) of a pregnant woman, and found the maximum similarity of the microbiome composition between the placenta and oral cavity. Representatives of *Proteobacteria* predominate in the placental microbiome. Such species as *Prevotella tannerae* and *Neisseria* are also frequently detected [47].

The similarity in the composition of the oral and placental microbiome implies, as mentioned earlier, the translocation of oral bacteria into the placenta. This may explain the fact that odontogenic (periodontitis) and tonsilogenic maternal infections increase the risk of preterm labor, pregnancy and delivery complications [64, 65]. The presence of certain bacteria within the oral microbiota (e.g. *Actinomyces naselundii*) is associated with lower birth weight and preterm labor, while the presence of lactobacilli is associated with higher birth weight and later labor [66].

MODE OF DELIVERY AND THE GUT MICROBIOME OF THE NEWBORN

Pregnancy and labor present the first major exposure of the complex maternal microbiota to an infant and ensure intergenerational transmission of the microbiome. Rupture of a chorioamniotic membrane makes possible contact of an infant with mother's vaginal and perineal microbes. It is no coincidence that prolonged labor poses a risk of infection of an infant with opportunistic microbiota [67].

Mature infants born naturally (vaginally) ingest representatives of the mother's vaginal and intestinal microbiota in small amounts. These are mainly bacteria of the genera *Prevotella, Sneathia* and *Lactobacillus*, belonging to the phylum *Firmicutes*, class *Bacilli* of the genus *Propionibacterium* (phylum *Actinobacteria*, class *Actinobacteria*) and family *Enterobacteriaceae* (phylum *Proteobacteria*, class *Gammaproteobacteria*) [68].

In other words, the gastrointestinal tract of a newborn is intensively populated by aerobic and facultative anaerobic bacteria, which, on the one hand, reduce the oxygen concentration in the intestine and prepare conditions for colonization by obligate anaerobes, and, on the other hand, show proinflammatory potential, which is accompanied by the development of mild intestinal inflammation and the presence of mucus in the transient stool of an infant. Abundant contamination of the newborn's bioniche with *Lactobacillus* spp., the main representatives of the vaginal microbiome, establishes protection against pathogenic and opportunistic microorganisms, as well as provides maximum compatibility with the subsequent intake of lactobacilli from breast milk.

From the end of the first week of life, the intestinal microbiome of an infant undergoes a transformation: the level of strict anaerobes such as *Bifidobacterium* (phylum *Actinobacteria*), *Bacteroidia* (phylum *Bacteroidetes*) and *Clostridia* (phylum *Firmicutes*) begins to dominate, leading to the suppression of aerobic bacteria and, to some extent, facultative anaerobes such as *Propionibacterium* and *Enterobacteriaceae*. Since then, the intestinal microbiota becomes very similar to the intestinal microbiota of a one-month-old infant if the infant receives breast milk [69–71].

The intestinal microbiota of the mother is generally considered to be the source of *Bifidobacterium* and *Bacteroidia* for the child. Thus, we inherit the primary microbiota from our mothers, grandmothers and further down the maternal line [72]. By the second year of life, the child's microbiota resembles the adult one [68].

There is accumulating evidence that the human gut ecosystem is critical in the establishment and maturation of immunobiologic reactivity [73]. The presence of fetal microorganisms and/or their molecular signatures stimulates the fetal mucosal

immune response and prepares fetal tissues for colonization after birth [74, 75].

A recent study demonstrated the presence of tissue-resident memory cell-like T cells in the human fetal intestine, which, when stimulated, secrete more proinflammatory cytokines than naive T cells [76]. These results suggest that the fetal intestine is exposed to foreign antigens, but it is still unknown whether these antigens are microbial.

Thus, the intestinal colonization pattern which has been established during the first week of life is ulteriorly reflected in the microbial community of the human intestinal microbiome through various factors (genetics, diet, environment, lifestyle, etc.) [77–80].

THE INFANT'S FEEDING PATTERN AND THE MICROBIOME

As mentioned above, mother's microbiome and the sanitary state of environment determine the nature of the primary colonization. Subsequently, the composition of the intestinal microbiota largely depends on the type of feeding.

Breast milk (BM) is the first optimally balanced product with a complex biochemical composition, received by the infant almost immediately after birth. BM remains the only nutritional substrate for the first 4–6 months.

BM protects an infant from infectious diseases during the first days of life and contributes to the reduction of mortality due to the presence of many specific and nonspecific defense components: T- and B-lymphocytes, plasma cells, immunoglobulins (primarily IgA) and antimicrobial enzymes (lysozyme and lactoferrin) [81].

It has been established that breastfeeding prevents chronic diseases such as diabetes mellitus [82], obesity, hypercholesterolemia [83]. Undoubtedly, BM serves as a significant factor in the formation of a "healthy" microbiome of the child, since it is the main source of symbiotic microorganisms (bifidobacteria, lactobacilli, enterococci). BM also contains substances with antimicrobial and prebiotic potential: β-lactose, α-lactalbumin, lactoferrin, oligosaccharides, nucleotides, nucleosides, sIgA, leukocytes, lysozyme, and others. [84–86].

Low levels of phosphorus, β-lactose, and short-chain fatty acids (SCFAs) reduce the pH of the intestinal environment, inhibiting the proliferative growth of opportunistic and pathogenic bacteria and providing an optimal titer of resident (obligate) BM microbiota (at least 10^3 CFU/mL of live bacteria and a wide range of bacterial DNA) [87].

There is no doubt that the intestinal microbiota of an exclusively breastfed child is characterized by a high level of bifidobacteria (90%) and low levels of *C. difficile* and *E. coli* [79]. However, it should be emphasized that for the first three days of the baby's life adult strains (*B. longum* and *B. catenulatum*) dominate the structure of bifidobacteria. However, they are substituted by infant strains (*B. infantis* and *B. breve*) by the second week under favorable conditions [88]. Studies conducted at the genetic and molecular level have established that the genome of infant bifidobacterial species contains 5 genes that encode the synthesis of bacterial galactosidases. For example, *B. infantis* produces the enzyme *β-galactosidases* and *B. breve* produces endogalactanase, which enable bifidobacteria to metabolize oligosaccharides contained in breast milk (BM) [89–91].

The dominance of infant strains of bifidobacteria contributes to the formation of immunologic tolerance, reduction of inflammation activity, and strengthening of the intestinal protective barrier. The above mentioned is illustrated by the work of Y.M. Sjögren et al. (2009). It was noted that by the end of the newborn period there was a direct correlation between the level of sIgA in intestinal secretion and the number of bifidobacteria, and an inverse correlation between the level of proinflammatory cytokine IL-6 and *Bacteroides* [92].

Nowadays, more than 400 different bacterial species, including staphylococci, lactic acid bacteria and bifidobacteria, have been isolated from BM samples. However, the cultured bacterial diversity detected in individual samples is much lower (2 to 8 different species per woman). Similar microbial species have been identified in the feces of infants, confirming the role of BM in bacterial colonization of the gut [93].

In general, the BM microbiome is quite complex. The identification of bacterial species using culture and molecular methods has identified cutaneous and gut-associated microorganisms such as *Staphylococcus, Streptococcus, Escherichia, Enterococcus, Veillonella, Prevotella, Pseudomonas* and *Clostridia* [94–99]. In addition, its dynamism and variability throughout lactation has been identified. Thus, the colostrum contains a large diversity of typical skin and intestinal-type microorganisms, whereas the microbiota in mature milk is less diverse and is represented by a significant number of infant oral bacteria and skin [100].

It is well known that the composition of the BM microbiome is modified by maternal factors: maternal somatic health, mode of delivery, stress, body mass index (BMI), antibiotic use, diet and place of residence [18, 29].

Leyva L. Lopez et al. (2021, 2022) evaluated the variability of the BM microbiota according to maternal age, BMI, stage of lactation, subclinical mastitis (SCM) and breastfeeding practices: exclusively breastfed, predominantly breastfed or mixed feeding. Breast milk samples (n=86) were studied by 16S rRNA sequencing. According to the results of molecular genetic analysis, the most numerous genus inhabiting BM was Streptococcus — 33.8%, almost 2–3 times less frequently isolated Pseudomonas — 18.7% and Sphingobium — 10.7%. The relative abundance of the represented genera correlated with maternal factors [101, 102].

First, *Lactobacillus, Streptococcus* (phyla *Firmicutes*) and bacteria of phyla *Actinobacteria* were significantly more prevalent in early lactation, whereas oral *Leptotrichia* (phyla *Bacteroidetes*) and environmental *Comamonas* (phyla *Pseudomonadota*) were more prevalent in established lactation.

Second, intense proliferative growth of *Streptococcus, Lactobacillus, Lactococcus, Lactococcus, Leuconostoc* and *Micrococcus* was observed in multiparous women compared to primaparous ones.

Third, a diverse microbiota characterized by higher levels of lactic acid bacteria (*Lactobacillus*, *Leuconostoc* and *Lactococcus*), *Leucobacter* and *Micrococcus* was found in mothers with optimal BMI (19–25) compared to mothers with altered BMI [101]. In addition, individual microbial communities differed according to the stage of lactation and feeding method. More differentiated microbial species were detected in BM samples of women who performed exclusive breast feeding during all periods of lactation, compared to BM samples of women who supplemented their infants (11 vs. 1 and 13 vs. 2, respectively). In addition, the former were significantly more likely to have commensal and lactic acid bacteria, including *Lactobacillus gasseri, Granulicatella elegans, Streptococcus mitis* and *Streptococcus* parasanguinis, compared to the latter at the beginning and end of lactation.

Thus, the addition of herbal teas and/or complementary foods to the infant's diet leads to a transformation of the BM microbiome as a result of decreasing the number of bacteria which contaminate breast milk from the infant's oral cavity and increasing the "environmentally friendly" bacteria which migrate into breast milk from the mother's intestine [102].

The study performed in China examined the variability of the BM microbiome according to the duration of lactation, age, maternal residence and the presence of gestational arterial hypertension syndrome (gestational AH) in different areas of China. The researchers found the highest microbial diversity in the colostrum, which gradually decreases and changes throughout lactation. Thus, at the phyla level, the numbers of *Proteobacteria* increased and *Firmicutes* showed the opposite trend; at the genus level, *Staphylococcus, Streptococcus, Acinetobacter, Pseudomonas* and *Lactobacillus* dominated in the milk samples and expressed certain variations during lactation. The geographical location of the mother significantly influenced the formation of the BM microbiota and the number of the predominant genus. In addition, milk from healthy mothers had more diverse microbial community at the genus level during early lactation than milk from mothers with gestational arterial hypertension [103].

Since BM microbiota is involved in the formation of infant's intestinal microbiome through initial GIT inoculation, it has been assigned a status — "Mother Nature's prototype probiotic food" [154]. Infants exclusively breastfed for the first 3–4 months of life, consuming about 800 ml of GM per day, receive ~10^5–10^7 CFU of bacteria from milk, which certainly determines the main species composition of the gut microbiome.

A cross-adoption experiment showed that it is the breastfeeding mother, not the biological one, who determines the composition of the infant's microbiome, which persists after weaning and over a lifetime [104]. As part of the Human Microbiome Project, T. Ding and P.D. Schloss (2014) further confirmed that breastfeeding in infancy is a major life cycle characteristic that influences bacterial composition in adults [105].

Non-exclusive models have been proposed to collect BM samples (Fig. 2).

1. *Transfer of microorganisms from maternal skin to breast milk.* Molecular approaches have been used for genetic typing of Gram-positive organisms contaminating both maternal and infant skin as well as breast milk in order to demonstrate the association of specific strains in the dyad [106, 107]. The nipple and areola are in the infant's oral cavity, resulting in the introduction of maternal skin-associated bacteria into the infant's mouth and gastrointestinal (GI) tract during breastfeeding [108].

2. *Retrograde flow of microorganisms from the infant's mouth to the mammary ducts* [97]. Based on the physiology of infant suckling, it is possible that there is a retrograde flow of breast milk from the infant's mouth through the nipple into the mammary gland [109, 110]. This mechanism explains the presence of *Gemella, Veillonella, Staphylococcus,* and *Streptococcus* microorganisms in both the in-

fants' oral cavity and breast milk [97, 111]. Other bacteria such as Actinomyces were not always detected in BM although they commonly inhabit the oral cavity of newborns. In addition, DNA signatures of bacteria were detected in initial samples of colostrum even before breastfeeding has started [98]. Thus, although milk transfer from the infant's oral cavity can explain the presence of some microbes, it cannot fully reveal the composition of the BM microbiota.

3. *An alternative model to explain the presence of typical intestinal microorganisms in the BM.* Dendritic cells (DCs) of the intestinal mucosa regularly ingest intestinal bacteria and transport them to local lymphoid follicles, where specific IgA is produced. DCs and immunoglobulin-secreting lymphocytes circulate in the blood but can selectively return to the intestine through interaction with β7-integrins and adhesion molecules secreted by endotheliocytes (adressins, MAdCAM-1). Mammary gland endothelial cells synthesize MAdCAM-1 molecules during pregnancy, allowing selective entry of "programmed" DCs containing gut bacteria into the gland. These microorganisms or their DNA, as well as DNA from other microorganisms, can directly enter the infant GIT and alter the structure of microbial communities, providing the basis for the *entero-mammalian tract* (EMT) model.

The EMT model is supported by three studies involving the mother and the preterm infant. A subset of genomic signatures corresponding to *Bifidobacterium longum, Streptococcus thermophilus* and *Bifidobacterium* pseudocatenulatum appeared to be shared by maternal stool, maternal blood, breast milk and infant stool samples [91, 106, 112]. Several studies also emphasize that some bacteria presented in the mother's gut are able to reach her mammary gland not only during lactation but also in late pregnancy through a mechanism involving intestinal dendritic cells and macrophages [113].

4. *Mechanism of microbiota transmission from mothers to breast milk by spreading from the mammary gland.* Experiments in a mouse model of cytomegalovirus (CMV, CMV) have demonstrated that viruses can remain dormant in the mammary gland after primary infection [114]. It is hypothesized that the process of lactation reactivates these viruses. In accordance with this idea, CMV has been detected in the BM of asymptomatic CMV seropositive women. Virolactia, the presence of live virus in the BM, correlates with the duration of lactation and peaks in the 3–4th week of lactation. It has been noted that CMV excretion was

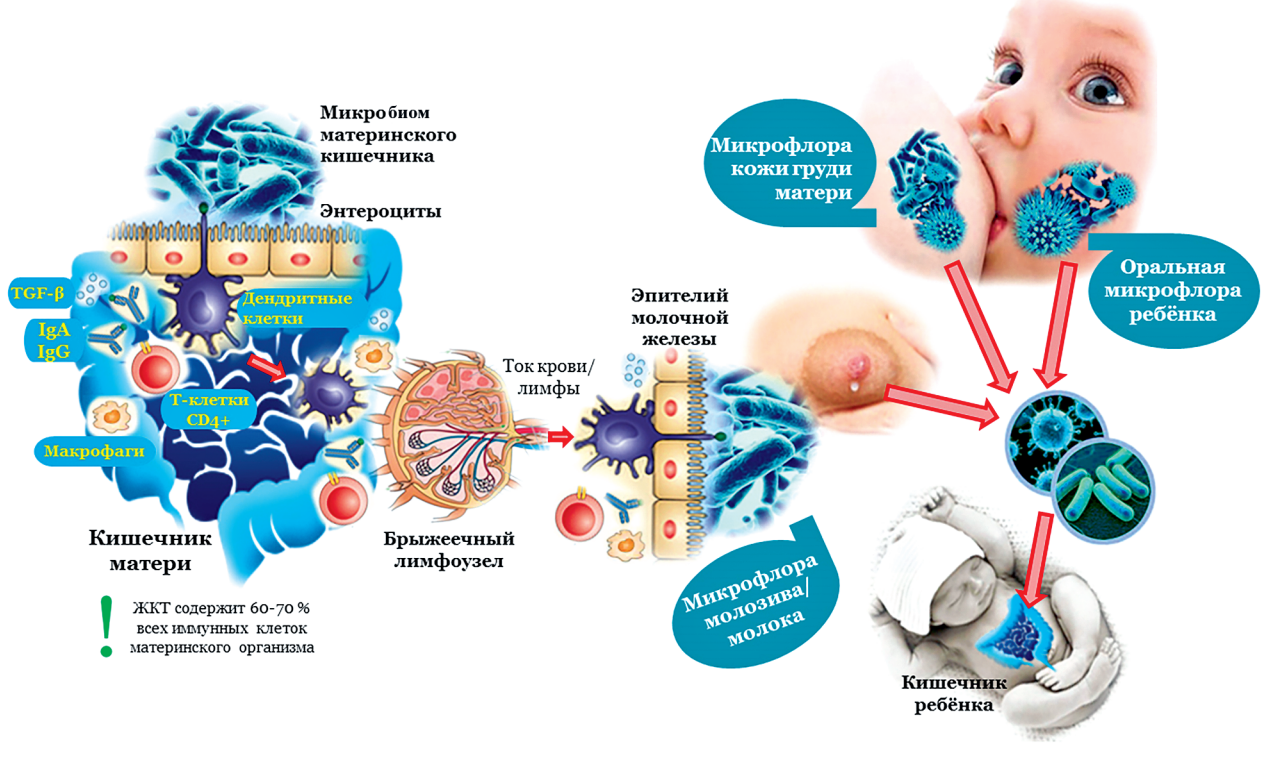

Fig. 2. Models of breast milk microbiome assembly (Source: Latuga MS, Stuebe A, Seed PC. A review of the source and function of microbiota in breast milk. Semin Reprod Med. 2014 Jan;32(1):68-73)

Рис. 2. Модели сборки микробиома грудного молока (Источник: Latuga MS, Stuebe A, Seed PC. A review of the source and function of microbiota in breast milk. Semin Reprod Med. 2014 Jan;32(1):68–73)

apparently restricted to breast milk [115]. Preterm infants may be at risk of postnatal CMV infection through breast milk as a result of reduced transplacental transmission of CMV antibodies [116]. Clinical evidence supports the fact that CMV excretion in mothers of preterm infants may depend on local immune factors in the mammary gland [117].

COMPLEMENTARY FOOD INTRODUCTION AND THE GUT MICROBIOME OF THE INFANT

The gradual introduction of complementary foods (CF) modifies the bacterial diversity in the infant gut. It has been noted that the gut microbiota becomes more complex since proliferative growth of bacteroidetes and other representatives of anaerobic microbiota is induced. Subsequently, the total number of bifidobacteria is suppressed and the species affiliation is transformed: infant species are being replaced by adult species such as *B. longum, B. adolescentis, and B. catenulatum* [118–122].

Along with genetically encoded nutritional factors, these changes in the gut microbiota determine gut ontogeny at the beginning of solid food intake [123]. For example, experiments in sterile mice have shown that bacterial colonization of the gut is required for the regulation of weaning-induced antimicrobial peptide expression [124]. In addition,this transition from breastfeeding to contemporary food promotes the formation of the intestinal barrier and induces profound intestinal remodeling [125–129].

Complementary foods introduce new substrates. Their assimilation requires bacterial populations with appropriate metabolic activity, which begins to remodel when solid food is introduced. It continues at least until the age of 3 years, microbial diversity parallelly increases [130].

Dietary enlargement is also accompanied by a restructuring of the immune status. An experimental work conducted on rats showed that weaning of suckers induced αβ-TCR(+) T cells in the lymphoid tissue associated with the intestine. Moreover, receptors to IL-2 were increased, these receptors may contribute to the development of allergic inflammation [131].

Bacterial hydrolysis products, primarily short-chain fatty acids (SCFAs), are known to play a modulatory role in metabolism and immunity in the child. Butyrate is an energy source for colonocytes. It maintains the integrity of the epithelium in the intestine [132]. In addition, it promotes Treg cell differentiation and suppresses inflammatory responses as shown in bacterial butyrate producers such as *Faecalibacterium prausnitzii* [130, 133, 134]. Propionate also potentiates *de novo* Treg cell formation in the periphery [133].

An experiment on suckling rabbits identified 29 metabolites. It revealed a strong modification of the cecal metabolome after the initiation of solid food intake. Thus, the concentration of short-chained fatty acids, the main bacterial metabolites, increased: 10-fold for butyrate, 5-fold for acetate and 2-fold for propionate. In addition, high concentrations of methanol and two sugars (glucose and ribose) were detected in cecum. The predicted relative number of microbial pathways involved in the production of propionate, acetate and butyrate increased.

Taking into account these results, the scientists suggested that changes in the cecal metabolome may be a signal which triggers the maturation of the epithelial intestinal barrier. The regulatory function of the blind intestinal mucosal transcriptome was assessed to confirm hypothesis presented.

In vitro metabolomic and transcriptomic analyses have demonstrated that the change in microbiota composition at the beginning of solid food intake is associated with a major shift in the production of bacterial metabolites that coincides with transcriptomic regulation of key components of both the immune and physical intestinal barrier. Metabolites of the intestinal microbiota, namely butyrate [135], partly induce the maturation of the intestinal barrier during weaning.

When the volume of BM is significantly less than solid food, the end of breastfeeding is accompanied by relative stability of microbial composition [136]. This period is notable for the appearance of adult intestinal bacteria representatives of *Bacteroidetes, Firmicutes* types and the *Clostridia class: Clostridium, Ruminococcus, Faecalibacterium, Roseburia* and *Anaerostipes* [118, 137].

Thus, microbial composition is usually highly unstable and lacks species diversity during the first year of life [138–140]. Nevertheless, a number of studies have shown that some bacteria which are common for adult microbiome colonize infants' GIT from the first months of life [106, 141].

ENVIRONMENTAL FACTORS AND THE GUT MICROBIOME OF THE INFANT

In the last decade it has been proven that the composition of intestinal microbiota is significantly influenced by the residence. It is explained by differences in the environmental situation, nutrition, lifestyle and traditions existing in a certain territory.

M. Fallani et al. (2010) conducted a multicenter study of the intestinal microbiome in infants from five European countries: Sweden, Scotland, Germany, Italy and Spain. The place of residence, mode of delivery, dietary patterns, and antibiotic use were studied for the fecal microbiota composition. Infants aged 6 weeks (n=606) were included into the study. It was established that the area of residence influenced the intestinal microbiota of infants as much as the mode of delivery or feeding did [142].

The researchers noted that children living in the north of Europe had higher levels of *Bifidobacteria*, *Atopobium, C. perfringens,* and *C. difficile*, while southern infants had higher levels of *Bacteroides, Eubacteria,* and *Lactobacillus*. Researchers concluded that differences in diet and lifestyle in different European countries may affect the formation of the child's intestinal microbiome [142].

Children born in poor areas of developing countries are exposed to microbial colonization earlier than infants in rich and highly developed societies. Thus, as there is no competition among bacteria of the genus *Enterobacter*, newborns living in high economic countries tend to be colonized by "skin bacteria" — *Staphylococcus epidermidis* [143]. This reformed colonization process, associated with increased hygiene measures, may have an irreparable impact on the development of both the overall microbiome and the immune system of infants.

The probability of sharing bacteria through household items and indoor air is shown to increase commensurately with the number of people living in a house. S.J. Song et al. (2013) found that members of the same family living together in a limited area have more similar microbiomes than relatives living separately [144]. The maximal relatedness of the skin microbiome among spouses is particularly indicative, as well as the sharing of surface bacterial communities between hosts and their dogs [92].

Such factors as prolonged living of a future mother in countryside, frequent contact of an infant with domestic animals and, consequently, with their microbiota in the first year of life, have a protective effect, increasing immunologic tolerance [145, 146]. Thus, growing up in a more diverse microbial ecosystem helps train a child's immune system not to overreact to triggers, and reduces the likelihood of asthma, allergies, and inflammatory bowel disease (IBD) [147–149].

Kindergarten is another external factor that contributes to the maturation and formation of the intestinal microbiome at an early age.

Three published studies have examined the relationship between kindergarten daycare and children's GIT microbiota [150–152]. The first study (Thompson A.L., 2015) indicated an increase in α diversity in children visiting kindergarten. The second (Hermes G.D.A., 2020) failed to demonstrate a significant contribution of attending a kindergarten in shaping the microbiome. The third (Mortensen M.S., 2018) — examined interindividual (β-diversity) and intraindividual (α-diversity) variability in microbiota, antibiotic and disease resistance in children aged 1–6 years.

The studies conducted had a completely different design, lacking: a comparison group (participants of appropriate age who did not attend kindergarten) and consideration of additional factors that significantly adjust the structure of the microbiome. As a result, completely different data were obtained, which did not allow us to conclude: whether a child's prolonged presence in kindergarten has an impact on the character of the intestinal microbiota and if there is the significance of this impact.

The tremendous work carried out under the guidance of A. Amir (2022) made a significant contribution to identify differences in the composition of the gut microbial ecosystem in organized and unorganized children. The researchers took into account all the shortcomings of previous experiments and expanded the list of additional factors. The study included children of different ages from four kindergartens, and a comparison group — children of the same age, but brought up at home. The material for analysis covered four time intervals and took into account the age of the child at the time of entering kindergarten and the length of time in an organized group. Overall, the cohorts did not differ significantly in demographic and test characteristics.

The longitudinal nature of the cohort of children made it possible to characterize the dynamics of gut microbial composition in organized young children as a small ecosystem. It is emphasized that, microbiome formation is much more influenced by the child's presence in a particular group than by the method of delivery and the nature of feeding, which are leading factors in the first year of life. The research shows that age is the dominant distorting factor in microbial composition not only in the first, but also in the second and third years of life. Other factors showing a modest, but significant contribution were the sex, the time of entry into kindergarten and the duration of attendance, as well as the mother's or child's receipt of antibiotics (both during and within 3 days after delivery),

the nature of feeding, and the age of introduction of solid food (the first complementary food).

It is proved that microbial composition of children attending kindergarten and non-organized (home) children differs. Enrichment of taxa is more often observed in children who visit the same kindergarten for a long period of time without changing the socializing group, compared to children of the same age who have not yet started attending a kindergarten. Taxa from the families *Bifidobacteriaceae* (q=0.04) *Actinobacteria type, Lactobacillaceae* (q=0.05) and *Staphylococcaceae* (q=0.05) of the *Firmicutes* type and *Pasteurellaceae* (q=0.04) of the Proteobacteria family type were significantly more frequently detected in children staying at home. Children visiting kindergaten had increased abundance of the family *Prevotellaceae* and genus *Prevotella* of the *Bacteroidetes* type (q=0.04), as well as *Lachnospiraceae* (q=0.05) and *Ruminococcaceae* (q=0.04) of the *Firmicutes* type.

In addition, the researchers confirmed once again that children of the same age from the same kindergarten are significantly more similar in their microbial landscape than children of the same age from two different kindergartens. Moreover, starting from the second month of attendance, children from the same kindergarten become more similar in their microbial composition. This means that a particular kindergarten contributes to the formation of a collective microbial pattern.

It was interesting to find that the frequency of early kindergarten attendance and the mix of children in the population had an inverse relationship with childhood diabetes. In turn, higher number of children in the group was positively associated with greater protection against diabetes. These data suggest that early exposure may play a role in the development of immunoregulatory mechanisms that protect against diabetes. However, further longitudinal studies are needed to investigate whether the patterns of gut microbial maturation and kindergarten attendance in healthy children are associated with future health and disease, as well as immunologic and allergic outcomes [153].

Thus, the gut microbiome is predominantly shaped by environmental factors, while genetics explains less than 10% of the variation. The first 3 years of life (early childhood) show the highest intra- and interindividual variability in the gut microbiome. It is no coincidence that this time is considered a "critical period" for the maturation of the gut microbiome.

Visiting organized groups is important for the formation of microbial composition in early childhood. A specific child care institution influences the gut microbiome, and the microcosm of each child acquires similar characteristics when regularly attending a child care center. In addition, the gut microbial composition of organized children differs from that of home-raised children. At the same time, enrichment of taxa is more often observed in children who stay in the same child care institution for a long time.

CONCLUSION

Thus, the data of the literature indicate that the formation of intestinal microflora of a child begins from the intrauterine stage and is a long, complex multifactorial process, the violation of which is associated with the development of various pathological conditions in children. A deeper understanding of the mechanism of intestinal microbiota formation in children will make it possible to develop effective methods of prevention and correction of microecological disorders in children and related diseases in different periods of life.

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