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ROLE OF THE INTESTINAL MICROBIOTA IN THE PATHOGENESIS OF MULTIPLE SCLEROSIS. Part 2. Gut microbiota as a predisposition factor for the multiple sclerosis development

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This part of the review focuses on the proposed involvement of the gut microbiota in the realization of the genetic risk of multiple sclerosis, the formation of the intestinal microbiome in early life, and provides data supporting the hypothesis that aberrant formation of the intestinal microbiota in early life may be a predisposing factor to multiple sclerosis.

Keywords: intestinal microbiome; genome; risk factors for multiple sclerosis; critical periods of ontogeny; environmental factors; micronutrients.

РОЛЬ МИКРОБИОТЫ КИШЕЧНИКА В ПАТОГЕНЕЗЕ РАССЕЯННОГО СКЛЕРОЗА. Часть 2. Кишечная микробиота как фактор предрасположенности к развитию рассеянного склероза

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В данной части обзора уделено внимание предполагаемому участию кишечной микробиоты в реализации генетического риска рассеянного склероза, формированию кишечного микробиома в ранней жизни, а также приводятся данные, поддерживающие гипотезу, что аберрантное формирование кишечной микробиоты на ранних этапах жизни может быть предрасполагающим фактором рассеянного склероза.

Ключевые слова: кишечный микробиом; геном; факторы риска рассеянного склероза; критические периоды онтогенеза; средовые факторы; микронутриенты.

Introduction

For most immune-mediated diseases, the gut microbiota is assumed to be involved in the realization of genetic risk; the disease develops in genetically predisposed individuals against the background of a certain composition of the gut microbiota. For example, certain risk alleles associated with inflammatory bowel diseases are only manifested when they are activated by the gut microbiome [1, 2]. Given that immunologically and metabolically the gut microbiota is integrated with the host [3] and the number of bacterial genes is hundreds of times greater than the number of host genes [4], its contribution to the genetic risk of diseases appears quite logical.

On the contrary, the gut microbiota is considered a complex polygenic factor influenced by combinations of host genomic loci and environmental factors [5]. While the main emphasis was previously placed on the influence of environmental factors,

List of abbreviations

EAE, experimental autoimmune encephalomyelitis; MS, multiple sclerosis

recently more attention has been paid to the genetic control of the composition of intestinal microbiota. Approximately 2%–8% of the intestinal microbiota is inherited [6], particularly families *Christensenellaceae* and *Methanobacteriaceae* [7] and bacterial taxa such as *Faecalibacterium*, an unclassified genus of families *Ruminococcaceae*, *Coprococcus, Bifidobacterium, Parabacteroides*, and *Bacteroides* [8–13]. In addition, associations of characteristic changes in the intestinal microbiome with disease risk genes in celiac disease, inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, and others have been identified [1, 2, 14–16].

Among the host candidate genes that can control the composition of the microbiome, immune response genes, genes regulating gut functions, and genes involved in metabolic processes are considered [17], which ensure an effective symbiosis between the host and microbiota and act as genetic risk factors for various diseases.

The following sections will present data on genes related to risk factors of multiple sclerosis (MS) or involved in the pathogenesis of the disease that is thought to be involved in controlling the composition of the gut microbiota.

Intestinal microbiota as a factor of genetic risk realization

Genetic control of intestinal microbiota composition

Over the past decade, research has demonstrated a close link between the host gut microbiota and health, which raises the question of how the gut microbiota is formed and whether host genes play a role in this process.

The influence of host genetic factors on intestinal microbial populations was demonstrated in experiments with reciprocal colonization of germ-free (GF) danio rerio or GF mice with intestinal microbiota from pathogen-free mice and fish species, respectively. It turned out that after 14 days, the taxa characteristic of the recipient species prevailed in the transplanted bacterial community [18].

The role of the genome in the control of the gut microbiome is also indicated by studies of monozygotic and dizygotic twins that have revealed greater similarity of microbial taxa among monozygotic twins than among dizygotic twins and twins compared with unrelated individuals [7, 19–23]. The gut microbiomes of twins differ if they live and eat in different households [7, 21].

How and to what extent the host controls the composition of the intestinal microbiota are currently unknown. It is assumed that the influence on the bacterial community inhabiting the gut is exerted through specific genetic loci controlling individual microbial species or a group of related taxa or through genetic loci exerting a pleiotropic effect on groups of relatively distant microorganisms, promoting the spread of those of them that benefit the host [5]. Host gene mutations can influence their interaction with the compositional and functional diversity of the microbiome, potentially modulating human susceptibility to disease [24].

Genes of innate immunity receptors, *toll-like receptors* (*TLRs*) and *nucleotide-binding oligomerization domain* (*NOD*)*-like receptors* (*NLRs*), are considered the most likely candidate genes because microorganisms are recognized through them and genes involved in *TLR*- and *NLR*-mediated signal transduction pathways (*Myd88*, *IRAK,* and others) [25, 26].

The activity of *TLR2*, which recognizes Gram-positive bacteria, correlates with the abundance of *Coriobacteriaceae* (p_*Actinobacteria*) and *Lactococcus* (p_*Firmicutes*) [5]. An abnormal increase in *Enterobacteriaceae* (p_*Proteobacteria*) is observed in mice lacking *TLR5*, which recognizes flagellin [27]. Moreover, comparative experiments on microbiota transfer in newborn and adult *Tlr5*-deficient mice show that the neonatal expression of *TLR5* affects the microbiota composition throughout life [28].

NOD2 loci are also associated with the abundance of *Enterobacteriaceae* [2]. In addition, the abundance of the representatives of *Bacteroidetes* increases in *NOD2-/-* mice [26, 29, 30], the abundance of *Alistipes* (f_*Rikenellaceae*) and *Bacteroides* (f_*Bacteroidaceae*) increased at the genus level, and the abundance of *Prevotella* (f_*Prevotellaceae*) decreased [30]. In another study in *NOD2-/-* mice, the abundance of *Faecalibacterium prausnitzii* decreased in the ileum and cecum [31].

When the adaptor protein *MyD88*, which mediates signal transduction from all *TLRs* except *TLR3*, was deficient, the *Firmicutes/Bacteroidetes* ratio decreased, and the abundance of *Lactobacillaceae, Rikenellaceae*, and *Porphyromonadaceae* increased in mouse intestines [32].

In addition to *TLRs* and *NLRs,* other receptors for innate immunity – *C-type lectins* and RIG-I-like receptors, are barely studied in relation to microbiome control.

Genes encoding antimicrobial peptides can also control intestinal bacterial populations [33]. The adaptive immune system evolved in vertebrates to regulate the abundance of beneficial microorganisms [34]; thus, the genes of the adaptive immune

response may be also involved in the genetic control of the diversity of the colonized microbiota, for example, *major histocompatibility complex II* (*MHCII*) or *human leucocyte antigen* (*HLA-DR*) genes, which are responsible for the presentation of antigens to T cells, and genes controlling the production and secretion of immunoglobulins into the intestinal lumen [30, 35–37].

To identify the genetic factors controlling the composition and functional diversity of the microbiome, microbiome genome-wide association studies (*mGWAS*) have been used recently. In these studies, many "immune" and "metabolic" host genes contributed to beta diversity (interindividual variability) and variability of the composition and functional composition of the intestinal microbiome. Forty-two host genetic loci that influence the beta diversity of the intestinal microbiome were identified, and the association of polymorphisms in several genes with the composition of the intestinal microbiome was revealed [38]. In particular, polymorphisms of *LCT* encoding lactase and *FUT2* encoding galactoside-2-alpha-L-fucosyltransferase 2 were found to be associated with the abundance and diversity of *Bifidobacterium* (p_*Actionbacteria*) [39, 40] and polymorphisms of *vitamin D receptor* (*VDR*) with the abundance of *Parabacteroides* (p_*Bacteroidetes*). *VDR-/-* mice had an increased abundance of *Parabacteroides* [38] and *Helicobacter hepaticus* (p_*Proteobacteria*) [41] and decreased abundance *Akkermansia muciniphila* (p_*Verrucomicrobia*) [41] compared with normal mice. *mGWAS* are discussed in detail in reviews [42, 43].

Although the data presented do not provide clear insights into the role of host genetic factors in controlling the composition of the gut microbiome, human genes and bacterial taxa play a role in the risk of the development or pathogenesis of MS [44].

Genome–microbiome interactions as a potential predisposition factor for MS

mGWAS have identified associations of genome–microbiome interactions in many diseases [45, 46], supporting the view that the microbiome is critical to host susceptibility/resistance to disease and, possibly, treatment response. Genome–microbiome associations have been identified for some autoimmune diseases, such as inflammatory bowel disease [2], rheumatoid arthritis [14]. However, no studies have been performed for MS. Nevertheless, evidence reveals the presence of this association in MS, since the genetically determined propensity for inflammatory processes can create a favorable environment for autoreactive T cells to initiate a specific immune response against autoantigens.

This assumption is supported by data [47] that female *TNF2* receptor-deficient mice (*Tnfr2-/- 2D2*) harbor in the fecal microbiome several *Bacteroides* spp., *Bacteroides uniformis*, and *Parabacteroides* spp., which predisposes them to the development of autoimmune demyelination of the central nervous system, compared with male mice with a different microbial background (*Akkermansia muciniphila*, *Sutterella* sp., *Oscillospira* spp., *Bacteroides acidifaciens,* and *Anaeroplasma* spp.

For other genes, associations with the intestinal microbiome composition have also been shown. For example, variants of certain loci of *VDR* [48, 49], which are associated with MS risk, are simultaneously associated with the modulation of the composition and metabolism of the gut microbiome [38], *VDR* expression protects the host from invasive pathogens and supports gut homeostasis, and gut bacteria activate *VDR* signal transduction [50]. *VDR* forms a heterodimeric complex with the *retinoid X receptor*, which mediates the action of several endogenous and exogenous ligands (vitamin D, secondary bile acids, and fatty acids) [51, 52]. In turn, bile acids act as key *VDR* ligands and regulators of *VDR* expression [53]. Interestingly, *Parabacteroides*, whose abundance varies with genetic *VDR* polymorphisms [38], contain genes involved in secondary bile acid metabolic pathways [54]. The abundance of *Parabacteroides* varies in several studies [55–58], as well as impaired bile acid metabolism in MS [59]. These findings indicate that these factors may be interrelated, and genome–microbiome interactions, in this case, *VDR* polymorphisms, bile acid metabolism, *Parabacteroides* abundance, and their contribution to the pool and regulation of bile acid metabolism may play significant roles in the pathogenesis of MS.

Table presents some associations of genes that control certain bacterial taxa within the intestinal microbiota and are also risk genes (or involved in the pathogenesis) of MS.

Characteristically, these genes control the colonization of bacterial taxa whose abundance is altered in patients with MS. On the contrary, the altered composition of the gut microbiome affects the type of immune response that is involved in modifying the gut microbiome [60, 61]. All this presents a combined effect of host genes and gut microbiome in both increasing the predisposition to MS and realizing the risk of MS development. That is, the intestinal microbiome acts as an environmental factor that directly interacts with the host genes to form

the disease phenotype and a genetically determined factor that is shaped by the host and interacts with it [62].

As shown in the table, the abundance of the same bacterial taxa can be affected by variations in different genes but with different vectors of changes or differently affect representatives belonging to the same phylum. For example, the abundance *of Bacteroidetes* changes when many *NLRs* (*NOD1, NOD2, NLRP12, NLRP3*, and *NLRP6)* are knocked out, and the abundance of *Bacteroides* increases when *NOD1* and *NOD2* are knocked out but decreases when *NLRP3* is knocked out. *NLRP3* knockout decreases the abundance of *Bacteroides* and increases the abundance of *Prevotella*. *TLR4* knockout decreases the abundance of *Alistipes* (p_*Bacteroidetes* f_*Rikenellaceae*), and *Myd88* knockout, which mediates signal transduction pathways from *TLRs*, increases the abundance of representatives of this phylum, *Rikenellaceae*, and *Porphyromonadaceae*. The abundance of *Parabacteroides* (p_*Bacteroidetes*) increases when *VDR is* knocked out.

The associations listed in Table 1 do not exhaust all the genome–microbiome interactions relevant to MS; future studies are likely to identify new associations and confirm or refute the significance of those already identified. For example, a recent study in patients with MS found a correlation between *BTF3L4*, a homolog of *BTF3*, a regulator of apoptosis, and abundance of *Lawsonella* (p_*Actinobacteria*; o_*Mycobacteriales*; *suborder Corynebacterineae*) [168]. *L. clevelandensis* was first isolated from abscesses [169] and found in amyotrophic lateral sclerosis in the nervous tissue [170]. Associations of genes involved in the synthesis and metabolism of B vitamins with the composition of the gut microbiome may be associated with the risk of MS development, especially in children [171].

Finally, the first study evaluating the interaction of the host genome with the intestinal microbiome in a model of experimental autoimmune encephalomyelitis (EAE) was recently published [172]. The influence of the host genome on the susceptibility to EAE and bacterial composition of the gut microbiome before disease onset has been demonstrated. In mice with 29 unique genotypes, the authors identified specific gut bacteria and their metabolic functions associated with lower or higher susceptibility to EAE in mice of several genotypes and showed that short-chain fatty acid metabolism was a key factor, with the ability of the commensal species *Lactobacillus reuteri* to exacerbate EAE [172]. These results demonstrate the existence of complex interactions between the host genome and gut microbiota that modulate the susceptibility to autoimmune diseases of the central nervous system. Understanding these interactions will provide future opportunities to develop strategies for modulating the gut microbiome and reducing the risk of developing not only MS but also other autoimmune diseases.

We also observed that the background initial microbiota predetermine the course of EAE in animals, and high levels of indigenous *Enterococcus* spp. is a necessary but not sufficient condition for resistance to disease development [71]. Thus, the reciprocal influence of the host genome on the microbiome composition and the regulatory influence of the microbiota inhabiting the gut on host gene activity may be a risk factor (predisposition) for MS.

Although the host genotype contributes to the formation of the gut microbial community, environmental influences at different periods can alter the microbiota profile [173]. The most sensitive and important period for the action of adverse factors may be the stage of gut microbiota formation.

Disruption of gut microbiota formation as an MS-predisposing factor

Formation of intestinal microbiota

The formation of the intestinal microbial community occurs during the first few years of life, a time that corresponds to the critical period of immune and nervous system development; therefore, the future health of an individual largely depends on which microorganisms will colonize various niches of the body during this period. The colonization of the intestine with microbiota is a dynamic process that occurs in a certain sequence according to the law of succession: facultative anaerobes such as enterobacteria (coliform bacteria) and lactobacilli colonized first, followed by anaerobic species such as bifidobacteria, bacteroides, clostridia, and eubacteria [174–176]. The first microorganisms are transmitted from the mother, a mechanism that ensures the acquisition of the "right" microorganisms necessary for the development of the infant's body. When exactly this process begins is currently under active research.

For many decades, the fetal gut was believed to be sterile, and the first microorganism-colonize the infant's body at birth from the mother and environment [177, 178].

Based on these ideas and the determination of microbiota using culturing methods, in 1983, Cooperstock and Zedd [179] distinguished four phases of early colonization of the infant gut: phase I, during

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Table / Таблица

Genes that control the composition of the gut microbiome and their association with the risk (pathogenesis) of multiple sclerosis
Гены, контролирующие состав кишечного микробиома, и их ассоциация с риском (патогенезом) рассеянного склероза

Gene	Association of the gene with the abundance of bacterial taxa	Changes in genome-controlled bacterial taxa in MS/EAE	Attitude toward risk (pathogenesis) of MS/EAE	
			Gene	Of a bacterial taxon
TLR2 (*toll-like receptor 2*)	*TLR2* correlates with f_*Coriobacteriaceae's* abundance and g_*Lactococcus* [5]	↑ f_*Coriobacteriaceae* [55, 63]	• ↑ *TLR2* response in MS [64]. • *TLR2* activation in the CNS contributes to inflammation in ER-PS and progression of EAE [65]. • In female *TLR2-/-* mice, the severity of EAE ↓ [66]. • In *TLR2-/-* mice, the severity of EAE is similar to that in *WT* mice [67]	• The negative effect of f_*Coriobacteriaceae* has been suggested [55, 63]. • *Coriobacteriales* more than double the risk of MS activity in children [68]. • The administration of *Hsp65*-producing *Lactococcus lactis* prevents EAE [69]
TLR5 (*toll-like receptor 5*)	At *TLR5-/-* ↑ f_*Enterobacteriaceae* [27]	• ↑ f_*Enterobacteriaceae* [55, 70]. • ↑ opportunistic species (*Citrobacter* spp., *Acinetobacter* spp.) f_*Enterobacteriaceae* [71]. • ↑ g_ *Acinetobacter* [72]	• *TLR5* expression is not increased in EAE in C57BL/6 mice [67]. • ↑ production of IL-12 and IL-6 by monocytes of patients with MS when stimulated by flagellin, a *TLR5* ligand [73]	• Cross-reactive antibodies specific to *Acinetobacter* species are elevated in the serum of patients with MS [74, 75]. • *Acinetobacter* 3-oxoadipate-CoAtransferase has homologous amino acid sequences with *MOG* and 4-car boxymuconolactondecarboxylase with *BMP* [76]
TLR4 (*toll-like receptor 4*)	At *TLR4-/-*: ↑ *Lachnospiraceae_NK4A136_group*; ↓ g_*Faecalibacterium*; ↓ g_*Alistipes*; ↓ g_*Bifidobacterium* [77]	• ↓ *Lachnospiraceae_NK4A136* [68, 78, 79]. • ↓ g_*Faecalibacterium* [56, 57, 79, 80–83]. • ↑ g_*Alistipes* [56]. • ↓ g_*Bifidobacterium* [57]. • ↑ g_*Bifidobacterium* [55, 80, 84, 85]	• *TLR4-/-* mice have ↑ the severity of EAE [86]. • In male C57Bl/6 *TLR4-/-* mice, ↑ the severity of EAE [66]. • *TLR4* contributes to the infiltration of Th17 cells in the CNS during EAE [87]	• *Lachnospiraceae_NK4A136* has a protective effect on MS in children [68]. • g_*Faecalibacterium* has a protective effect on MS [56, 57, 79, 80–83]. • ↑ g_*Alistipes* in the chronic phase of encephalomyelitis associated with demyelination in mice infected with the Theiler virus [88]. • *Bifidobacterium* levels correlate with disease severity [89]. • *Bifidobacterium adolescentis* promotes *Th17* differentiation in the intestine of mice [90]. • *Bifidobacterium adolescentis* aggravates autoimmune arthritis in mice [90]

Table continuation / Продолжение таблицы

Gene	Association of the gene with the abundance of bacterial taxa	Changes in genome-controlled bacterial taxa in MS/EAE	Attitude toward risk (pathogenesis) of MS/EAE	
			Gene	Of a bacterial taxon
NOD1 (*Nucleotide-binding oligomerization domain-containing protein 1*)	↑ o_*Clostiridiales*; ↑ g_*Bacteroides*; ↑ f_*Enterobacteriaceae* [91, 92]	• ↑ o_*Clostridiales* [93]. • ↑ c_*Clostridia* [94, 95]. • ↑ g_*Bacteroides* [55, 57]. • ↑ f_*Enterobacteriaceae* [55, 70]	*NOD1-/-* mice are EAE-resistant [96]	• *Clostridium perfringens* ε-toxin promotes demyelination [97]. • A course of administration of *Bacteroides fragilis* reduces the severity of EAE in mice [98]. • ↑ f_*Enterobacteriaceae* has a proinflammatory effect [55, 70]
NOD2 (*Nucleotide-binding oligomerization domain-containing protein 2*)	*NOD2* gene polymorphism affects: – ↑ f_*Enterobactericea* [2]; – ↑ g_*Bacteroides* [26]; – ↑ g_*Dorea* [26]; – ↑ g_*Subdoligranulum* [26]; – ↓ *Faecalibacterium prausnitzii* [99]	• ↑ f_*Enterobacteriaceae* [55, 70]. • ↑ g_*Bacteroides* [55, 57]. • ↑ g_*Dorea* [58, 94, 100]. • ↓ g_*Dorea* [83]. • ↓ g_*Subdoligranulum* [78]. • ↓ *Faecalibacterium prausnitzii* [56, 57, 80–83]	*NOD2-/-* mice are EAE-resistant [96]	• ↑ f_*Enterobacteriaceae* has a proinflammatory effect [55, 70]. • g_*Bacteroides* has a protective effect by promoting *Treg* differentiation [98]. • g_*Dorea* (f_*Lachnospiraceae*) produces formic acid, inhibits the growth of *Enterobacteriaceae* [101], and can have a proinflammatory effect by promoting the production of IFNγ [102]. • g_*Subdoligranulum* is associated with MS [103]. • *Faecalibacterium prausnitzii* has a protective effect by producing butyrate and stimulating Treg differentiation [56, 57, 80–83]
NLRP12 (*NLR* [*NOD-like receptor*] *family pyrin domain containing 12*)	At *NLRP12-/-*: – ↓ o_*Bacteroidales*; – ↓ o_*Clostridiales*; – ↓ f_*Lachnospiraceae*; – ↑ f_*Erysipelotrichaceae* [104]	• ↓ in MS: – g_*Bacteroides* [80, 81, 105]; – c_*Clostridia* [80]; – f_*Lachnospiraceae* [93, 100] • ↑ in MS: – f_*Erysipelotrichaceae*; – *Erysipelotrichacea_unclas* [78]; – g_*Holdemania* [94]; – g_*Turicibacter* [78]; – g_*Catenibacterium* [55]	• A p.*Leu972His* mutation in the sixth LRR domain of *NRLP12* is associated with familial MS [106]. • In *NLRP12-/-* mice, ↑ the severity of EAE [107]. • In *NLRP12-/-* mice, EAE with atypical symptoms (ataxia and balance disorder) [107–109]	• g_*Bacteroides* has a protective effect by promoting *Treg* differentiation [98]. • f_*Erysipelotrichaceae* (g_*Holdemania*, g_*Turicibacter*, g_*Catenibacterium*, *Erysipelotrichaceae_unclas*) are increased in MS and are considered harmful in MS [55, 78, 94]. • c_*Clostridia* has protective butyrate-producing species [80, 94, 95, 105], but there are also pathogenic ones (*C. perfringens*) [97]. • f_*Lachnospiraceae* can have dual effects, both anti-and proinflammatory [110]

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NLRP1 (*NLR Family Pyrin Domain Containing 1*)	In *NLRP1-/-* mice: ↑ o_*Clostridiales*; ↑ f_*Lachnospiraceae*; ↑ g_*Oscillospira*; ↑ g_*Ruminococcus* [111]	• ↑ f_*Lachnospiraceae* [55]. • ↑ g_*Blautia* [55, 83, 94, 100]. • ↑ g_*Dorea* [58, 94, 100]. • ↑ g_*Coprococcus* [55, 58, 81]. • ↑ c_*Clostridia* [94, 95]. • ↑ o_*Clostridiales* [93]. • ↑ g_*Oscillospira* [55]. • ↑ g_*Ruminococcus* [55, 56, 81, 85]	• Homozygous mutations (p.*Ile601Phe* or p.*Ser1387Ile*) ↑ the risk of MS [112], a homozygous missense variant in *NLRP1* (*Gly587Ser*; p) is associated with familial MS [113]. • Associations of several heterozygous *NLRP1* mutations in patients with MS have been identified [114]	• ↑ c_*Clostridia* [94, 95]. • ↓ f_*Lachnospiraceae* [100]. • g_*Blautia* is presumed to have proinflammatory effects on MS, but there are protective species [55, 82, 93]. • g_*Coprococcus* is involved in the regulation of intestinal permeability and suppression of TNFα expression [115]. • *Coprococcus* butyrate producers show neuroprotective activity in Parkinson's disease [116]. • ↑ g_*Oscillospira* assumed to have a negative effect [55]. • Mucin-degrading *Ruminococcus* increases in inflammatory diseases [117]
NLRP3 (*NLR Family Pyrin Domain Containing 3*)	At *NLRP3-/-*: ↓ g_*Bacteroides*; ↑ g_*Prevotella*; ↑ g_*Desulphovibrio*; ↑ g_*Rumonococcus*; ↑ g_*Oscillospira* [118]	• ↓ g_*Bacteroides* [80, 81, 105]. • ↑ g_*Desulphovibrio* [55]. • ↓ g_*Prevotella* [80, 100]. • ↑ *Prevotella copri* [55]. • ↑ *Prevotella stercorea* [55]. • ↓ g_*Prevotella* [81, 100]. • ↑ g_*Ruminococcus* [55, 56, 81, 85]. • ↑ g_*Oscillospira* [55]	• *NLRP3* activation promotes MS/EAE progression [119, 120]. • *NLRP3* is associated with the response to IFN-β treatment in patients with MS with EAE mice [121]. • *NLRP3-/-* mice are EAE-resistant [120]. • In *NLRP3-/-* mice, ↓ the severity of EAE [122]	• *Bacteroides* produce lipid 654, which regulates the innate immune response [123], and propionate, which has an anti-inflammatory effect [124]. • ↓ g_*Bacteroides* are associated with inflammation in the gut [125]. • The negative role of ↑ g_*Desulphovibrio* is suggested [55, 63, 126]. • *Prevotella histicola* attenuates inflammation and reduces the severity of EAE [127]. • *Prevotella copri* aggravates inflammation in arthritis [128]. • *Ruminococcus* correlates with TNFα, IL-6, and IL-17 and is associated with decreased vitamin D levels [129]
NLRP6 (*NLR Family Pyrin Domain Containing 6*)	At *NLRP6-/-*: ↑ *Prevotellaceae*_g; ↑ g_*Prevotella*; ↑ p_TM7; ↓ g_*Lactobacillus* [130]	• ↑ *Prevotella stercorea* [51]. • ↓ g_*Lactobacillus* [74, 100]	• *NLRP6* is an important regulator of homeostasis in the gut [130]. • *NLRP6* can have a protective effect in chronic inflammation and a detrimental effect in acute inflammation [131]	• ↑ *Prevotella stercorea* in MS, a proinflammatory role is assumed [55]. • *Prevotella copri* is associated with the onset of rheumatoid arthritis [132]. • *TM7* ↑ on the Mediterranean diet [133], which is recommended for MS, *TM7* ↓ for cancer [133]. • *Lactobacillus* has strain-specific protective effects on EAE and MS [134, 135]

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Gene	Association of the gene with the abundance of bacterial taxa	Changes in genome-controlled bacterial taxa in MS/EAE	Attitude toward risk (pathogenesis) of MS/EAE	
			Gene	Of a bacterial taxon
Myd88 (*Myeloid differentiation primary response 88*)	Under *Myd88-/-*: • ↓ *Firmicutes/Bacteroidetes* ratio; • ↑ f_*Lactobacillaceae*; • ↑ f_*Rikenellaceae*; • ↑ f_*Porphyromonadaceae* [32]; • ↑ g_*SFB* [136]	• Reduced *Firmicutes/Bacteroidetes* ratio. • ↑ in MS: – g_*Lactobacillus* [55, 56, 105]; – f_*Rikenellaceae* MS/EAE [55, 137]; – f_*Porphyromonadaceae* [57]. • ↓ in MS: – ↑ f_*Rikenellaceae* [93]	*MyD88-/-* mice have ↓ severity of EAE [66, 67, 86]	• The administration of a mixture of lactobacilli reduced the severity of EAE [134]. • *Alistipes* (f_*Rikenellaceae*) uses tryptophan and exacerbates EAE by stimulating Th17 responses [138]. • *Porphyromonas gingivalis* (f_*Porphyromonadaceae*) is involved in complement-dependent inflammation [139] and impairs epithelial barrier function [140]. • The administration of *SFB* to GF mice led to the development of EAE by inducing Th17 cells [141]
HLA MHCII	• *MHC II class* variants in mice and fish are associated with different intestinal microbiota [142]. • In *MHC II-/-* mice: ↓ g_*Lactobacillus*; ↑ g_*SFB*; ↑ g_*Helicobacter* [143]	• ↑ g_*Lactobacillus*. • ↓ g_*Lactobacillus*. • *Helicobacter pylori* is more common in patients with MS than in healthy individuals [144]	• The presence of the DRB1*15.01 allele increases three times the risk of MS [145]. • HLA-DRB1*0301 and HLA-DRB1*1303 alleles ↑ the risk of MS [146, 147]. • The HLA-A*0201 allele is protective [146]	• *HLA* polymorphism modulates the course of EAE and gut microbiota [148]. • *Helicobacter pylori*-infected patients have a milder course of MS [149, 150]. • *Helicobacter pylori* infection reduces the severity of EAE in mice [151]. • *SFB* aggravates EAE [141]
LCT (*Lactase*)	• The *LCT* gene polymorphism rs4988235 is associated with the abundance of *Bifidobacterium longum* [39]. • The *SNP* at the *LCT* locus correlates with the abundance of g_*Bifidobacterium* [17, 152, 153]. • ↑ abundance of *Bifidobacterium longum* [39]	In MS ↑ g_*Bifidobacterium* [80, 84, 85, 154]	The rs4988235 (LCT-13910 C > T) variant associated with higher milk intake is associated with ↓ MS risk [155]	• *Bifidobacterium* levels correlate with disease severity [89]. • *Bifidobacterium adolescentis* promotes Th17 differentiation in the intestine of mice [90]. • *Bifidobacterium adolescentis* aggravates autoimmune arthritis in mice [91]

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FUT2 (*Fucosyl-transferase 2*)	FUT2 variants are related: • ↓ g_*Faecalibacterium* and ↑ p_*Proteobacteria* [156]; • ↓ *Blautia* and ↑ *Rikenellaceae*, *Peptostreptococcaceae*, *Clostridiales* and *Turicibacter* [157]; • With the abundance of *Ruminococcus torques* [153]	• ↑ p_*Proteobacteria* [158]. • ↓ p_*Proteobacteria* [85, 93]. • ↓ *Sutterella* (p_*Proteobacteria*) [159]. • ↑ *Ruminococcus torques* [43]	–	• ↑ *Psuedomonas, Mycoplana, Haemophilus,* and *Acinetobacter* (p_*Proteobacteria*) contribute to inflammation [92]. • Transplantation of microbiota from patients with MS with decreased *Sutterella* into GF mice caused a more severe course of EAE than microbiota transplantation from healthy mice [159]. • *Ruminococcus torques* negatively correlate with the abundance of *Treg* cells in RA [160]
VDR (*vitamin D receptor*)	• *VDR* gene variants are associated with β-diversity [38]. • *VDR* gene polymorphism is associated with *Parabacterioides* abundance [38]. • At *VDR-/-* ↑ *Parabacteroides* [38]	↓ g_*Parabacteroides* [72, 100, 161, 162]	The *ApaI* polymorphism of *VDR* may confer different susceptibility to MS in different populations [49, 163]	• g_*Parabacteroides* are involved in the metabolism of phytoestrogens and bile acids, which are *VDR* ligands and regulate *VDR* expression [72]. • g_*Parabacteroides* stimulate *Treg* differentiation [72]
PLD1 (*Phospholipasa D1*)	*SNP* in the *PLD1* gene in humans are associated with *Akkermansia muciniphila* levels [8]	↑ *Akkermansia muciniphila* [57, 72, 137]	• *PLD1* levels ↓ in the plasma of patients with RR-PS [164]. • In *PDL-/-* mice the severity of EAE ↓ [165]. • ↑ *PLD1* expression in rat CNS at the peak of EAE and ↑ abundance of PLD1-positive cells in EAE lesions [166]	• *Akkermansia muciniphila* stimulates the Th1-type immune response [72]. • Can have both pro- and anti-inflammatory effects [167]

N o t e: CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; ER-PS, secondary-progressive type of multiple sclerosis; RR-PS, remitting–relapsing type of multiple sclerosis; ↑, increase; ↓, decrease.

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the first 2 weeks after birth; phase II, breastfeeding period; phase III, from the beginning of complementary feeding until complete cessation of breastfeeding; and phase IV, until complete complementary feeding, and introduction to adult diet. However, results of sequencing technologies to identify microorganisms show that intestinal microbiome formation can occur in utero due to maternal microorganisms in the placenta and amniotic fluid [180–183]. Although not yet universally accepted and debated, these findings demonstrate the importance of the maternal microbiome for the initial stages of infant gut microbiome formation [184].

Bacteria have been detected in the umbilical cord blood [185], amniotic fluid [186–188], and fetal membranes [188, 189] of healthy women who have given birth without signs of inflammation. For example, *Proteobacteria* (*Ralstonia insidiosa*), *Firmicutes* (*Lactobacillus rhamnosus, Lactobacillus crispatus, Lactobacillus iners*), and *Actinobacteria* (*Bifidobacterium* spp.) were found in the placenta and amniotic fluid [180–183].

How microorganisms enter the placenta and amniotic fluid is uncertain. They may be translocated from the mother's oral cavity and intestines through the bloodstream or with dendritic cells, which absorb bacteria from the intestinal lumen and transport them throughout the body during migration to lymphoid organs [190, 191]. In particular, a similar mechanism has been described in mice [192]. However, whether these microorganisms establish themselves in the fetal intestine or whether their presence is transient is unclear.

The meconium (first stool after birth) of infants defines a complex community of microbes, although less diverse than adult feces [185, 193]. The presence of typical gastrointestinal representatives such as *Enterococcus* spp. and *Escherichia coli* in the meconium [185, 193] indicates that these microorganisms enter the infant's intestine intrauterus.

Immunological tolerance is required for the successful colonization of the infant's gut with microorganisms, which is also provided by the mother through the preferential induction of regulatory T lymphocytes [194]. The maternal gut microbiome changes during pregnancy, adapting to the stage of fetal development [195]: In the first trimester, the abundance of *Faecalibacterium prausnitzii* increases, promoting the formation of T-regulatory cells (Tregs), which provide immunological tolerance to the fetus; in contrast, in the third trimester, the abundance of *Enterobacteriaceae, Enterococcaceae,* and *Streptococcaceae*, facultative anaerobic microorganisms that are transmitted to the infant either intrauterine or at birth and dominate the gut microbial community during the first days of its life, increases. Since the infant receives microorganisms at birth when passing through the maternal delivery canal [174, 196–198], the meconium microbiome of newborns is unsurprisingly very similar to the mother's vaginal microbiome [199]. However, the similarity in the microbial composition of the meconium of children born vaginally and by cesarean section may indicate that these microorganisms may have entered the intestines of the children while they were still *in utero*.

The second stage of maternal microbiota transmission occurs during breastfeeding [200, 201]. Between 100 and 600 bacterial species belonging to eight genera, namely, *Staphylococcus, Streptococcus, Serratia, Pseudomonas, Corynebacterium, Ralstonia, Propionibacterium, Sphingomonas*, and the *Bradyrhizobiaceae* family were found in the breast milk of healthy women [202]. These bacterial taxa constituted approximately half of the entire microbiome and were present in all samples, forming a common part of the microbiome. The remaining part of the microbiome (variable) was represented by microorganisms found in individual breast milk samples in different combinations [202].

During the lactation period, the bacterial composition of breast milk changes. Milk produced immediately after delivery (colostrum) contains more lactic acid bacteria along with staphylococci, streptococci, and lactococci. After 6 months of lactation, the abundance of species colonizing the oral cavity (*Veillonella* spp., *Leptotrichia* spp., and *Prevotella* spp.) increases in breast milk, possibly to prepare the baby for the transition to solid food [203].

In general, the gut microbiota of newborns is characterized by an unstable structure and has a limited set of bacterial taxa, which becomes more complex with increasing food diversity [204, 205]. Thus, the introduction of additional food to breast milk is associated with an increase in the diversity of the bacterial community and a change in the predominant bacterial phyla. At 6 months of age, *Bacteroidetes* and *Firmicutes* begin to dominate the human fecal microbiota, and *Verrucomicrobia* appear; by contrast, *Proteobacteria* and aerobic Gram-negative bacteria significantly decreased [206].

The composition of the intestinal microbiota stabilizes by the end of the first year of life, acquiring the features of the adult gut microbiome [206–208]. During this period, nutritional and environmental factors become more important in maintaining the

diversity of the child's gut microbiome composition than those of the mother.

Although the gut microbiota in 3-year-old children is already similar to that in adults [175, 206, 209], it reaches its maximum diversity only in adolescence [210].

Intestinal microbiocenosis is unique in each person, and under normal (eubiotic) conditions, it is a complex balanced ecosystem in which microorganisms are in a symbiotic relationship with the host. However, some factors can affect intestinal microbiome formation. These factors include premature birth, cesarean section, artificial feeding, early weaning, antibiotic use, stress, and infections [211, 212].

The phases of intestinal microbiome formation and factors that affect this process are summarized in the figure.

The aberrant formation of the intestinal microbiome in the early stages of development is thought to result in changes in its functional properties, which can lead to long-term epigenetic changes, metabolic, and immunological dysregulation, structural and functional changes in the immune and nervous systems, and disorders of the intestinal and blood–brain barrier [213, 214] and can further contribute to increased susceptibility to various diseases [215, 216] including MS.

Environmental factors affecting the formation of gut microbiota and their relationship to MS risk

Among environmental factors that have the greatest influence on the composition of the gut microbial community, exposures in early life (maternal factors, mode of birth, gestational age, feeding type, weaning age, and antibiotic use), diet, and micronutrients, stress, and lifestyle (see figure) are discussed.

Relatively few studies have reported the influence of maternal and perinatal factors. In particular, a potential association between gestational diabetes and maternal overweight/obesity with MS before pregnancy was noted [217]. Metabolic disorders are accompanied by changes in gut microbiome composition [218]; diet, antibiotic intake, high glucocorticoid levels due to stress, infectious or immune-mediated exposures during pregnancy, or lactation can also lead to gut microbiome dysbiosis and affect the formation of gut microbiota composition in infants [218]. In turn, impaired gut microbiome formation in early life is associated with an increased risk of autoimmune disease development later in life [219–222].

Emerging evidence shows that the influence of the maternal microbiome on the development of the immune system of offspring begins in utero. In this respect, of interest are the studies that showed the long-term effects of gut bacteria, limited to the gestation period, on the immune profiles of cubs when GF-pregnant females were colonized with a genetically modified strain (HA107) of *E. coli*, which did not replicate and was eventually eliminated from the gut [223]. The maternal microbiota controls the expression of several genes in the intestinal mucosa, prepares the intestines of calves for postnatal microbial colonization, and affects the innate but not the adaptive link of immunity. Previously, long-term immune changes are believed to be associated with the action of the newborn's microbiota in the postnatal period [224]. That is, the maternal microbiome forms both the composition of the intestinal microbiome and immune functions in the offspring at an early age.

Although the mechanisms of these effects are currently not fully established, the long-term consequences of adverse perinatal influences on the immune system and increased risk for immune-mediated diseases may be associated with epigenetic changes [225], and embryogenesis is a particularly vulnerable period for DNA modifications [226, 227]. Since the gut microbiota is involved in the epigenetic regulation of Th17/Treg balance [228], the absence or excess of certain microorganisms in the maternal microbiome during this period can lead to the dysregulation of gene expression/activity.

In the EAE model reproducing the pathological processes and symptoms characteristic of MS, a more severe disease course was observed in the adult offspring of mice that were exposed to pathogens during pregnancy. These mice showed increased production of Th17 cells and proinflammatory cytokines, which proves the long-term effect of gestational exposure on immune responses in the offspring [229, 230]. Systemic administration of high doses of lipopolysaccharide to pregnant females led to similar effects [231]. In another study [232], pregnant rats received a mixture of antibiotics added to drink water 2 weeks before delivery and 4 weeks after delivery. This exposure altered the microbial profile in the offspring of antibiotic-treated rats and exacerbated the EAE course when the rats reached 3 months of age. Evidence shows that the administration of antibiotics to adult animals reduces the severity of EAE symptoms [233–235].

A pilot study [236] in children with MS revealed an association between perinatal exposure to pesticides and an increased risk of MS development. Pesticides are thought to have the strongest effect on

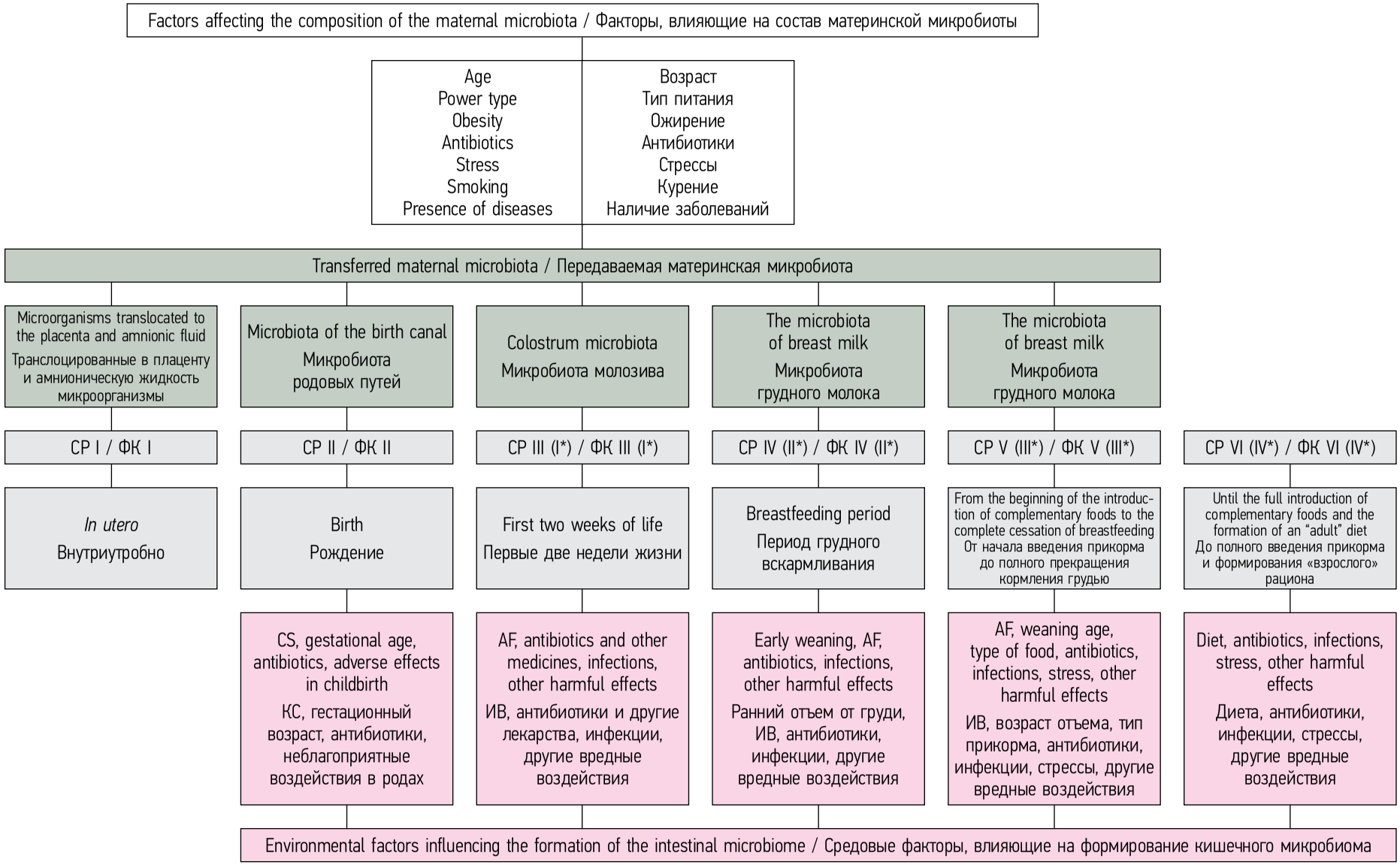

Figure. Phases of early infant colonization (modified by M.S. Cooperstock and A.J. Zedd [179]) and factors influencing this process. CP, colonization phase; CS, caesarean section; AF, artificial feeding. *Early colonization phases

Рисунок. Фазы ранней колонизации кишечника младенца (модификация M.S. Cooperstock и A.J. Zedd [179]) и влияющие на этот процесс факторы. ФК — фаза колонизации; КС — кесарево сечение; ИВ — искусственное вскармливание. *Фазы ранней колонизации

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the development of lymphoid organs during embryogenesis or early childhood [237, 238], which leads to long-term immune dysfunction and may contribute to the early development of MS.

At different gestational periods, the composition of the microbiome (intestinal and vaginal) of the mother changes; therefore, in the case of premature birth, the microbial composition of the mother's microbiome is not quite ready for transmission, which is confirmed by significant differences in the microbiota of preterm and term-born infants. Thus, premature infants lacked two major bacterial genera in the gut microbiota observed in term-born infants: *Bifidobacterium* and *Lactobacillus*, with compensatory dominance of *Proteobacteria*. In addition, *Clostridium difficile*, *Bacillus*, and *Staphylococcus* bacteria were found [239, 240]. A higher incidence of MS was noted in people born prematurely compared with those born at term [241], although another study [242] did not find such a pattern.

Several studies link the risk of MS development to impaired intestinal microbiocenosis formation due to factors such as cesarean section [243], artificial feeding [244], and exposure to antibiotics in early life [245, 246].

The normal dynamics of bacterial colonization of the gut are disrupted in cesarean births, which can lead to an abnormal immune system [247]. The gut microbial composition of infants born by cesarean section resembles that of the maternal skin microbiota, with the dominance of *Staphylococcus, Corynebacterium*, and *Propionibacterium*, whereas that of naturally born babies is dominated by *Lactobacillus, Prevotella*, and *Sneathia* [198]. Differences in the structure of the bacterial community in the intestine are noted not only within a few months [198, 248, 249] or a year [174, 248, 249] but persist into the 7th year [250] and even into adulthood [249, 251].

Women who underwent cesarean sections usually receive prophylactic antibiotics before delivery; thus, microbiota disturbances in babies born by cesarean section reflect the cumulative effect of both the altered mode of delivery and antibiotic exposure [252].

Conflicting data present the association of the mode of delivery (vaginally or cesarean section) with the risk of MS development. Some studies have shown that cesarean section may be a risk factor for both early onset (in childhood) of MS [253] and an increased risk for MS [236, 243]. Other studies have found no risk [243, 254] or even observed a reduced risk of childhood MS [236]. A study of children with MS reported significant differences in the type and abundance of bacterial taxa in the gut compared with healthy children. In particular, *Christensenellaceae*, which is thought to be an inherited bacterial taxon [7], may be relevant to the mode of birth and affect MS risk [55, 63, 93]; however, no study has revealed as to which genes control the abundance of this family.

The feeding type during the neonatal period also affects the gut microbial composition of infants, which is a possible risk factor for MS. Breast milk is the first dietary exposure in infancy, contains various protective compounds including carbohydrates, nucleotides, fatty acids, vitamins, immunoglobulins, cytokines, immune cells, lysozyme, lactoferrin, and other immunomodulatory factors [255, 256], and is a rich source of bacteria including lactic acid bacteria, propionic bacteria, bifidobacteria [257]. Breast milk oligosaccharides stimulate specific intestinal microbiota, block pathogen adhesion sites in the gut, and/or act as analogs of soluble pathogen receptors [258, 259]. Breast milk bacteria – *Bifidobacterium, Lactobacillus*, and *Enterococcus* – are an important source of gut bacteria for infants, and they can contribute to the normal development of the immune system by competitive exclusion of pathogenic bacteria, increased production of antimicrobial peptides, and improved function of the gut barrier [257]. The intestinal microbiota of breastfed infants has more Bifidobacteria and Lactobacilli, whereas *Bacteroides* spp., *Clostridium*, *Streptococcus*, *Enterobacter*, *Citrobacter*, and *Veillonella* predominate in formula-fed infants [260–263]. The significance of the presence of *Bifidobacterium* during this period for MS resistance is confirmed by the fact that the administration of *Bifidobacterium animalis* to rats during lactation contributed to a milder course of adult-induced EAE [264]. Interestingly, *Lactobacillus casei Shirota*, also administered during lactation, did not have a protective effect and increased the disease duration [265], which once again emphasizes the importance of the presence of bifidobacteria in this period of ontogenesis.

Evidence shows that breastfeeding reduces MS risk in children and adults [266, 267], whereas reducing the duration of breastfeeding and artificial feeding increases MS risk, including in children [253, 266, 268, 269]. However, Graves et al. [236] have not confirmed the protective effect of breastfeeding on MS development.

After birth, the development of the immune and nervous systems continues for the first 2–3 years of life [270], and the gut microbiota plays an important

role in these processes as it stimulates the development of immune responses, which in turn inhibit microbiota growth [271]. Because naïve T cells (Th0) differentiate into subsets of Th1 (supporting cellular immune responses), Th2 (supporting humoral and allergic responses), and Th17 (involved in autoimmune processes) [270], impaired microbiota composition early in life can affect host immune status and can be a risk factor for disease, including MS [272, 273].

Lipopolysaccharides of different bacterial species have different structures and immunogenic properties, and children from areas with a higher prevalence of autoimmune diseases have dominance of bacterial species that produce less immunogenic lipopolysaccharides, which may affect the "training" of the immune system in early life, increasing disease susceptibility [274]. The injection of lipopolysaccharides in the neonatal period (P3 and P5 rats or P15 mice) promoted an easier course of EAE in later life, in contrast to prenatal exposure [231], which was accompanied by increased corticosterone levels [275] or more Tregs [276]. The administration of subpyrogenic doses of the proinflammatory cytokine IL-1β to rats at different periods of early postnatal ontogenesis (at 1, 2, 3, or 4 weeks of life) differently affects the EAE course in adults. Thus, the administration of IL-1β at P1–P7 and P22–P28 worsened the EAE course, and at P8–P14, and P15–P21, it attenuated disease severity compared with the corresponding control group [277]. The neonatal administration of dexamethasone (at P1, P2, and P3) to rats aggravated the EAE course in adult rats [278], as did neonatal stress [279, 280]. Early age stress had a long-term effect on immune functions and exacerbated the EAE course in adult rats [280–282] and mice [283], and more pronounced effects were observed in males than in females.

Although the aforementioned studies did not investigate the composition of the intestinal microbiota, prenatal stress, or increased glucocorticoids during this period affects the composition of the offspring microbiota. Thus, in prenatally stressed animals, the abundance of *Lactobacillus* was reduced and those of *Oscillibacter*, *Anaerotruncus*, and *Peptococcus* increased [284]. Infants of mothers with high cortisol levels during pregnancy were characterized by a lower abundance of lactic acid bacteria and a higher abundance of *Proteobacteria*, among which other pathogens are present (*Serratia, Citrobacter*, and *Enterobacter*) [285], and their abundance increases in MS [44]. In female rhesus macaque cubs that experienced acoustic stress during pregnancy or separation stress in early life, intestinal colonization with microbiota was impaired [286, 287].

Early antibiotic treatment delays microbiota maturation in infancy [288]. In a population-based study of over 776,000 newborns in Denmark, antibiotic use before and during pregnancy correlated with an increased risk of offspring susceptibility to infection in childhood [289]. The administration of antibiotics during the neonatal period (P7–P23) altered the gut microbiota profile and myelin structures in adult mice [290].

Epidemiological evidence presents that sunlight exposure and vitamin D (VitD) intake during pregnancy and early childhood may influence MS risk [291]. Although VitD deficiency in females during pregnancy resulted in reduced EAE severity in the offspring [292], the effect of gestational VitD deficiency on the EAE course was evident in the second generation of mice, which developed a more severe disease course [293]. The importance of normal VitD levels in early life has been demonstrated in experiments with VitD supplementation in rats from birth to weaning (before puberty) in which EAE severity was reduced in later life [294]. Moreover, VitD supplementation precisely at an early age, and not during pregnancy, or as an adult, contributed to the suppression of EAE [295], which indicates the existence of a critical period for the effects of VitD on MS.

The deficiency of B vitamins (folic acid and cyanocobalamin) during the critical window (1000 days) can affect the maturation of the gut microbiota and its interaction with the host, with consequences on adolescence and adulthood [296]. The supplementation of pregnant mice with methyl donors (betaine, choline, folic acid, and vitamin B_{12}) resulted in significant differences in the composition of the postnatal gut microbiota compared with the microbiota of the offspring of mice without supplementation [297]. The addition of methyl donors (folic acid and vitamin B_{12}) increases the pool of single-carbon fragments and changes the methylation of an individual gene locus in mice [298] and humans [299], affecting epigenetic regulation. Importantly, some microorganisms can synthesize various vitamins; however, the significance of this vitamin pool in the formation of the intestinal microbiota and interactions with the host is currently unknown [300].

Essentially, many factors can influence the formation of the intestinal microbiome and its properties in the prenatal and early postnatal period, forming a predisposition to disease in later life.

Conclusion

MS is a multifactorial disease in which genetic predisposition and environmental factors play a role. To date, how risk factors act during development has not been understood. Importantly, the critical age was 0–6 months, which is not only a period of vulnerability but also the most effective "window" for manipulating the composition of the microbiota to maintain and improve effective immune responses [300] and reduce disease risk. The studies mentioned in the review demonstrate that impaired gut microbiota formation has long-term consequences and can increase susceptibility to MS, and correction of gut microbiota composition early in life can be a strategy to reduce MS risk.

Additional information

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