DOI: 10.29326/2304-196X-2021-1-36-68-71
UDC 619:579.62:599

Review article: key aspects of mammal microbiome development

E. V. Semenova[1], O. A. Manzhurina[2], Yu. S. Parkhomenko[3]
FSBSI "All-Russian Veterinary Research Institute of Pathology, Pharmacology and Therapy" (FSBSI "ARVRIPP&T"), Voronezh, Russia
[1] *ORCID 0000-0002-7456-0647, e-mail: elenasemenova1992@gmail.com*
[2] *ORCID 0000-0003-0147-8965, e-mail: manol65@mail.ru*
[3] *ORCID 0000-0002-1460-5022, e-mail: yuliyasp21@mail.ru*

SUMMARY
This review article summarizes current understanding of the microbiota development in neonatal mammals based on the results of modern experimental studies in animals focusing on three aspects: initial colonization, microbiota effect on the immune function of the developing newborn animal intestine and external factors influencing the microbiome shaping during the juvenile period. The presented study results confirm that the microbial landscape correction is the most important factor for animal health improvement since healthy microflora contributes to the intestinal infection frequency and intensity reduction, and this, in turn, minimizes the use of antibiotics. The microbiome is known to have an impact on the immune system development, metabolic processes and even on the ethology, so an atypical microbial population can cause immune and metabolic disorders. The active interaction between microorganisms and the host organism begins already at birth. Even different modes of delivery (caesarean or vaginal delivery) may determine the initial colonization of the newborn. The animal genetics, nutrition and environment also influence the intestinal microbiota development. In this regard, further studies of probiotics are important to understand their efficacy for diarrhea prevention and treatment, their use as an alternative to antibiotics as well as for enhancement of the animal resistance to stress factors.

Keywords: Intestinal microbiome, colonization, mammals, young animals, livestock animals.

For citation: Semenova E. V., Manzhurina O. A., Parkhomenko Yu. S. Review article: key aspects of mammal microbiome development. *Veterinary Science Today*. 2021; 1 (36): 68–71. DOI: 10.29326/2304-196X-2021-1-36-68-71.

Conflict of interest: The authors declare no conflict of interest.

For correspondence: Yuliya S. Parkhomenko, Junior Researcher, Laboratory for the Diagnosis of Infectious and Invasive Diseases of the Scientific and Testing Center, FSBSI "ARVRIPP&T", 394000, Russia, Voronezh, Lomonosova str., 114 b, *e-mail: yuliyasp21@mail.ru.*

УДК 619:579.62:599

Обзор: ключевые моменты в процессе становления микробиома млекопитающих

Е. В. Семенова[1], О. А. Манжурина[2], Ю. С. Пархоменко[3]
ФГБНУ «Всероссийский научно-исследовательский ветеринарный институт патологии, фармакологии и терапии» (ФГБНУ «ВНИВИПФиТ»), г. Воронеж, Россия
[1] *ORCID 0000-0002-7456-0647, e-mail: elenasemenova1992@gmail.com*
[2] *ORCID 0000-0003-0147-8965, e-mail: manol65@mail.ru*
[3] *ORCID 0000-0002-1460-5022, e-mail: yuliyasp21@mail.ru*

РЕЗЮМЕ
Данный обзор направлен на обобщение современного понимания становления микробиоты новорожденных млекопитающих на основе результатов современных исследований в экспериментах с животными в трех аспектах, включая начальную колонизацию, влияние микробиоты на иммунную функцию кишечника развивающегося новорожденного и воздействие внешних факторов на формирование микробиома в ювенильный период. Результаты представленных в статье исследований подтверждают, что коррекция микробного пейзажа – важнейший фактор улучшения здоровья животного с учетом того, что именно здоровая микрофлора способствует снижению частоты и интенсивности кишечных инфекций, а это, в свою очередь, минимизирует использование антибиотиков. Известно, что микробиом влияет на развитие иммунной системы, метаболические процессы и даже на этологию, в связи с чем нетипичная микробная популяция способна вызвать нарушения как иммунитета, так и метаболизма организма. Активный процесс взаимодействия микроорганизмов и организма хозяина начинается уже при рождении. Даже различные способы родов – кесарево или вагинальное родоразрешение – могут определять начальную колонизацию новорожденного. Кроме того, на формирование микробиоты кишечника влияют генетика особи, питание и окружающая среда. В связи с этим актуально изучение пробиотиков – понимание их эффективности при профилактике и лечении диареи, использование как альтернативы антибиотикам, а также для повышения устойчивости животных к стрессовым факторам.

Ключевые слова: Микробиом кишечника, колонизация, млекопитающие, молодняк, сельскохозяйственные животные.

Для цитирования: Семенова Е. В., Манжурина О. А., Пархоменко Ю. С. Обзор: ключевые моменты в процессе становления микробиома млекопитающих. *Ветеринария сегодня*. 2021; 1 (36): 68–71. DOI: 10.29326/2304-196X-2021-1-36-68-71.

Конфликт интересов: Авторы заявляют об отсутствии конфликта интересов.

Для корреспонденции: Пархоменко Юлия Сергеевна, младший научный сотрудник лаборатории диагностики инфекционных и инвазионных болезней НИЦ ФГБНУ «ВНИВИПФиТ», 394000, Россия, г. Воронеж, ул. Ломоносова, 114 б, *email: yuliyasp21@mail.ru.*

INTRODUCTION

On livestock farms, gastro-intestinal pathology in young animals is the most significant economic factor causing financial losses as compared to other diseases. Diarrhea affects the fluid and nutrient absorption that contributes to growth impairment and overall negative effect on the animal health. Furthermore, if not treated promptly, this disorder rapidly spreads in the animal population and can result in high mortality [1].

Currently, diarrhea is commonly prevented with antibiotics against pathogenic bacteria being frequent diarrhea causes. A significant disadvantage of antibiotic use is emerging and spread of antimicrobial-resistant microorganism strains [2]. In large livestock holdings, bacteria rapidly acquire resistance genes due to constant presence of large numbers of animals in the limited space [3]. Therefore, effective and justified alternative for antimicrobial prevention of diarrhea in young livestock is required.

Many studies allow us to consider the gut microbiota as an important factor for the immune function development and the newborn health support. From this point of view, the intestinal microbiome determines the young animal health and resistance to intestinal infections. Nevertheless, the mechanisms of the microbiota impact on the immune and metabolic process development and establishment are largely undetermined [4].

Even Louis Pasteur has suggested that the microbiota has an important effect on the mammals' life. Animals as hosts have abundant and diverse population of microorganisms directly influencing the mechanisms of such biological processes as immunity and metabolism [5].

MICROFLORA EFFECT ON IMMUNE SYSTEM DEVELOPMENT

Host-microflora interaction plays a vital role in appropriate immune system development. Many researchers believe that the critical period for animals starts immediately after their birth when microbial antigen exposure is required for the immunity development [5–7]. Microflora has an impact on the immune system phylogenesis, onthogenetic development patterns of mucosal and general immunity as well as on anti-infective response effectiveness and adequacy. Various disorders during the body microbiota establishment, especially in gastro-intestinal tract, result in immune-dependent diseases [7]. This is confirmed by the studies of the immune system in sterile animals having poorly developed mucosa-associated lymphoid tissue, hypoplastic peyer's patches and characterized by decreasing numbers of CD4+-lymphocytes and IgA-producing plazmacytes in the mucosa lamina propria, and at the same time, by the shift in the T-cell differentiation towards type 2 T-helper cells in the lymphoid organs and decreased γ-interferon production [6, 8].

During the experiment in sterile mice H. Sokol et al. demonstrated that microflora-free mice developed atypical cytokine response to orally administered treated lipopolysaccharide (immune response-activating macromolecule of outer membrane of gram-negative bacteria) as compared to normal mice having gut microflora. Described atypical response differed from normal response in its delayed development followed by excessive cytokine release. In addition, sterile juvenile mice treated with *Bifidobacterium infantis* were found to be capable of return to normal cytokine response whereas in adult mice treated with the same probiotic the immune response failed to normalize. Thus, it was demonstrated that the sterile animals could not resist to pathogens [5]. Importance of own normal microflora development at early age for avoiding immune system malfunctions in future was demonstrated.

In their studies, I. H. Ismail et al. showed that the microbiome disorders in young animals could later result in autoimmune diseases, including allergy. At the same time, the authors demonstrated that the development of these pathological conditions could be minimized by probiotics [9].

FACTOR INFLUENCING MICROBIOTA ESTABLISHING

Currently, newborn mammals are believed to be sterile, and the initial microbial colonization of their bodies can occur during and immediately after their birth, when microbes first interact with the body and colonize it. Since this process is rapid, it is supposed to start in the birth canal or at the first environmental exposure of the newborns in the case of a caesarean section [6, 10, 11].

Contamination of environment objects with pathogenic and opportunistic microorganisms often has a negative impact on the animal microflora development resulting in decrease in obligatory microorganisms in its gastrointestinal biotope. During the experiment in Holstein and black-and-white calves, Russian researchers detected *Bifidobacterium* spp. in 1 g feces (diluted at 10^{-3}–10^{-10}) from clinically healthy animals whereas the said microorganisms were not detected in animals with diarrhea, toxemia and dehydration. In addition, a decrease in lacto-positive *Escherichia coli* strains and increase in lactose-negative enetrobacteria and bacteria with low lactase activity were observed as well as hemolytic *Escherichia coli* strains were detected in diseased animals [12].

In general, microbiota establishment is a dynamic process following the initial colonization that depends on such factors as host genetics, diet, maternal stress, interaction with the environment, early exposure to antibiotics [13].

In particular, the macroorganism genetics determine the intestine microenvironment that, in turn, influences the suitability of the internal environment for microbial colonization. Z. A. Khachatryan et al. detected an apparent association between gene mutations and relevant changes in the intestinal microflora characterized by depletion of the total bacteria number, loss of diversity and significant quantitative changes in the populations of some bacteria [14]. Nevertheless, no genetic association between intestinal microbiota and long-term growth and weight indicators has not been yet detected that requires further investigations in this field.

In addition, prenatal maternal stress could have an impact on the offspring intestinal microflora composition. According to D. Zhou et al., the dam's physiological parameters change during this period including a rapid heartbeat and stress hormone release. Moreover, the dam's behavior may change with increase or decrease in her appetite and activity. Such changes may have an impact on dam's microflora and potentially on the initial colonization of her offspring at birth. Maternal stress can also result in increase in cytokine concentration and, as consequence, in inflammation than affects the developing fetus causing changes in the fetus immune function [15].

MICROBIOTA EFFECT ON ETHOLOGY AND ADAPTATION

N. Sudo et al. presented evidence on the association of microorganisms with host behavioral responses based on the results of comparative tests of sterile mice and mice colonized with bacteria. To test the hypothesis that postpartum microbial colonization may have an impact on the development of the brain plasticity, the researchers compared the hypothalamic-pituitary response at different stress levels in two groups of genetically identical mice. Mice of one group were sterile and mice in other group were colonized with the specific bacteria. During the experiment, the mice were placed in 50 ml conical tube for one hour or in glass container covered with ether-soaked filter paper for 2.5 minutes. Sterile mice demonstrated more intensive stress response as compared to the mice with microflora. Moreover, decreased stress response was observed in the sterile mice following *Bifidobacterium infantis* probiotic administration [16].

In other studies, P. Bercik et al. detected that administration of antimicrobials to the mice colonized by the complete intestinal microbial community impaired the intestinal microbiota composition and enhanced the response to the stress factor. Therewith, the same antimicrobials administered to sterile mice had no impact on their behavior [17]. The study results demonstrated a potential association between intestinal microflora and animal behavior.

Experiment results published by M. Vijay-Kumar et al. showed the microbiota impact on the host metabolic dysfunction. Toll-like receptor 5 (TLR5)-deficient mice were used for the experiments. The said membrane protein is known to play a key role in gut innate immunity and to participate in pathogenesis of obesity-associated chronic inflammation. Then, the microbiota of these mice were inoculated to sterile wild-type mice. Significant hyperphagia and progressing metabolic disorder were observe in tested TLR5-deficient mice. Sterile wild-type mice colonized with the microbial strains derived from the intestines of the TLR5-deficient mice immediately manifested distinct changes in their intestinal microbiota, and then signs of the metabolic syndrome (obesity) [18]. The changes in microbe-free mice body constitution from normal to obese after colonization by the specific microbial population suggests that the gut microbiota could affect the host's metabolic functions.

CONCLUSION

Microbial colonization of young animals has a significant impact on their physiology and performance. The intestinal microflora and its proper development, particularly at a young age, can significantly determine the further functioning of certain systems, as well as act as a potential tool for reducing the diarrhea incidence in young livestock animals [1]. In this regard, studies of probiotics are of the most importance. It is important to understand how effective probiotics are for diarrhea prevention and treatment, whether they can serve as a full-fledged alternative to antibiotics, and whether they can be used to enhance animals' resistance to stress factors. Impact of dam's genetics and body state on her offspring microbiota formation is also important. Given the fact that the intestinal microbial landscape is a very mobile and fragile system, use of antimicrobial drugs for preventive purposes should be avoided.

REFERENCES

1. Abe F., Ishibashi N., Shimamura S. Effects of administration of bifidobacteria and lactic acid bacteria to newborn calves and piglets. *J. Dairy Sci*. 1995; 78 (12): 2838–2846. DOI: 10.3168/jds.S0022-0302(95)76914-4.

2. Shakhov A. G., Sashnina L. Yu., Lebedev M. I., Lebedeva Ye. V. Study of resistance of bacterial exciters of gastro-intestinal and respiratory diseases in piglets to antimicrobial preparations. *Russian Agricultural Sciences*. 2011; 2: 53–55. eLIBRARY ID: 15594622. (in Russian)

3. Manzhurina O. A., Skogoreva A. M., Romashov B. V., Romashova N. B. Modern trends in antibiotic resistance of the microbiota of domestic and wild animals. *Bulletin VSAU*. 2017; 1 (52): 41–45. DOI: 10.17238/issn2071-2243.2017.1.41. (in Russian)

4. Subbotin V. V. Study of the development of intestinal microbial population of weaned animals. *Proceedings of the 1st Congress of Russian Veterinary Pharmacologists.* [*Materialy Pervogo s"ezda veterinarnyh farmakologov Rossii*]. 2007; 570-575. Available at: http://zoovet.info/vet-knigi/123-farmakologiya/veterinarnaya-farm/6716-stanovlenie-normalnogo-mikrobiotsenoza-v-postnatalnom-periode-u-domashnikh-zhivotnykh. (in Russian)

5. Sokol H., Pigneur B., Watterlot L., Lakhdari O., Bermudez-Humaran L. G., Gratadoux J. J., et al. *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc.Natl. Acad. Sci*. 2008; 105 (43): 16731–16736. DOI: 10.1073/pnas.0804812105.

6. Mazmanian S. K., Liu C. H., Tzianabos A. O., Kasper D. L. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell.* 2005; 122 (1): 107–118. DOI: 10.1016/j.cell.2005.05.007.

7. Sjögren Y. M., Tomicic S., Lundberg A., Böttcher M. F., Björkstén B., Sverremark-Ekström E., Jenmalm M. C. Influence of early gut microbiota on the maturation of childhood mucosal and systemic immune responses. *Clin. Exp. Allergy*. 2009; 39 (12): 1842–1851. DOI: 10.1111/j.1365-2222.2009.03326.x.

8. Macpherson A. J., Harris N. L. Interactions between commensal intestinal bacteria and the immune system. *Nat. Rev. Immunol.* 2004; 4 (6): 478–485. DOI: 10.1038/nri1373.

9. Ismail I. H., Oppedisano F., Joseph S. J., Boyle R. J., Licciardi P. V., Robins-Browne R. M., Tang M. L. Reduced gut microbial diversity in early life is associated with later development of eczema but not atopy in high-risk infants. *Pediatr. Allergy Immunol*. 2012; 23 (7): 674–681. DOI: 10.1111/j.1399-3038.2012.01328.x.

10. Rutayisire E., Huang K., Liu Y., Tao F. The mode of delivery affects the diversity and colonization pattern of the gut microbiota during the first year of infants' life: a systematic review. *BMC Gastroenterol*. 2016; 16 (1):86. DOI: 10.1186/s12876-016-0498-0.

11. Shakhov A. G., Sashina L. Yu., Fedosov D. V., Erina T. E., Alekhin Yu. N. Intestinal microbiosis in hypotrophic milk-fed calves. *Agricultural Biology* [*Sel'skokhozyaistvennaya Biologiya*]. 2014; 49 (2): 105–111. DOI: 10.15389/agrobiology.2014.2.105eng. (in Russian)

12. Motorygin A. V., Lenchenko E. M. Methods of determination of qualitative and quantitative composition of microorganisms during intestine dysbacteriosis in calves. *Agricultural Biology* [*Sel'skokhozyaistvennaya Biologiya*]. 2011; 46 (2): 103–107. eLIBRARY ID: 16220466. (in Russian)

13. Laursen M. F., Andersen L. B., Michaelsen K. F., Mølgaard C., Trolle E., Bahl M. I., Licht T. R. Infant gut microbiota development is driven by transition to family foods independent of maternal obesity. *mSphere*. 2016; 1 (1):e00069-15. DOI: 10.1128/mSphere.00069-15.

14. Khachatryan Z. A., Ktsoyan Z. A., Manukyan G. P., Kelly D., Ghazaryan K. A., Aminov R. I. Predominant role of host genetics in controlling the composition of gut microbiota. *PLoS One*. 2008; 3 (8):e3064. DOI: 10.1371/journal.pone.0003064.

15. Zhou D., Zhang H., Bai Z., Zhang A., Bai F., Luo X., et al. Exposure to soil, house dust and decaying plants increases gut microbial diversity and decreases serum immunoglobulin E levels in BALB/c mice. *Environ Microbiol*. 2016; 18 (5): 1326–1337. DOI: 10.1111/1462-2920.12895.

16. Sudo N., Chida Y., Aiba Y., Sonoda J., Oyama N., Yu X. N., Kubo C., Koga Y. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *J. Physiol*. 2004; 558 (Pt 1): 263–275. DOI: 10.1113/jphysiol.2004.063388.

17. Bercik P., Denou E., Collins J., Jackson W., Lu J., Jury J., et al. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. *Gastroenterology*. 2011; 141 (2): 599–609. DOI: 10.1053/j.gastro.2011.04.052.

18. Vijay-Kumar M., Aitken J. D., Carvalho F. A., Cullender T. C., Mwangi S., Srinivasan S., et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science*. 2010; 328 (5975): 228–231. DOI: 10.1126/science.1179721.

Received on 25.11.2020
Approved for publication on 11.01.2021

INFORMATION ABOUT THE AUTHORS / ИНФОРМАЦИЯ ОБ АВТОРАХ

Elena V. Semenova, Junior Researcher, Laboratory for the Diagnosis of Infectious and Invasive Diseases of the Scientific and Testing Center, FSBSI "ARVRIPP&T", Voronezh, Russia.

Olga A. Manzhurina, Candidate of Science (Veterinary Medicine), Associate Professor, Head of the Laboratory for the Diagnosis of Infectious and Invasive Diseases of the Scientific and Testing Center, FSBSI "ARVRIPP&T", Voronezh, Russia.

Yuliya S. Parkhomenko, Junior Researcher, Laboratory for the Diagnosis of Infectious and Invasive Diseases of the Scientific and Testing Center, FSBSI "ARVRIPP&T", Voronezh, Russia.

Семенова Елена Вячеславовна, младший научный сотрудник лаборатории диагностики инфекционных и инвазионных болезней НИЦ ФГБНУ «ВНИВИПФиТ», г. Воронеж, Россия.

Манжурина Ольга Алексеевна, кандидат ветеринарных наук, доцент, заведующий лабораторией диагностики инфекционных и инвазионных болезней НИЦ ФГБНУ «ВНИВИПФиТ», г. Воронеж, Россия.

Пархоменко Юлия Сергеевна, младший научный сотрудник лаборатории диагностики инфекционных и инвазионных болезней НИЦ ФГБНУ «ВНИВИПФиТ», г. Воронеж, Россия.