Khazar Journal of Science and Technology
© Khazar University Press 2022
Volume 7 №2 2023, 35-53
DOI: 10.5782/2520-6133.2023.7.2.35

Phages and Immunity

Jamila Talibova[1], Matanat Novruzova[2], Safada Taghiyeva[2], Sara Gurbanova[2], Fakhraddin Shikhaliyev[2]

[1]Children's Rehabilitation Center of the Scientific Research Pediatric Institute named after K.Y. Farajova, Baku, Azerbaijan
[2]Department of Medical Microbiology and Immunology, Azerbaijan Medical University, Baku, Azerbaijan
Corresponding author: Safada.tagiyeva@yahoo.com

Abstract

In recent years, the microbiome and its role in the pathophysiology of diseases and the development of other human pathophysiological conditions have attracted great interest. Only recently has the presence of bacteriophages been identified in the microbiome and their potential role in maintaining normal immunity. The progress of our knowledge in this area opens up completely new perspectives for understanding the normal physiology of the human body, the treatment of diseases, including the most difficult ones for modern medicine. Of particular interest are studies of the interaction of the microbiome with the immune system.

Keywords: phages; immunity; pathophysiology; microbiome; lymphocytes**.**

Introduction

According to the current situation of COVID-19 pandemia in over the world detailed and deep investigation of the human immun system, formulation and adaptation of its components to the environment factors such us different microbial and non-microbial agression to the organism is very important. The topic have great actuality not only for medicals, but for all biology specialists.

Localisation and occurance of the phages to the intestine

The increased interest to the microbiome and the application of advanced sequencing technologies have provided possibility to assess the impact of the microbiome in the pathophysiology of the disease and its potential modulation for therapeutic purposes (Hargreaves et al., 2014). Interactions between the intestinal immune system, the

epithelial barrier, and bacteria residing on it are fundamental to maintaining healthy intestine homeostasis (Erez et al., 2017; Jain et al., 2017). The microbiota plays an important role in the formation of the human immune system. For example, inter-individual differences in responses to vaccines, chemotherapy, and immunomodulatory agents depend on differences in the gut microbiota. From the discovery of phages 100 years ago until the end of the 20th century, the vast majority of research focused on the well-known antibacterial effect of phages. Although phages have been used for immunization and to assess humoral immunity in animals and patients with immunodeficiency syndromes, there are no data on the interaction of phages with the immune system and the potential consequences of such events for the formation of the immune system (Burcelin, 2016; Sausset et al., 2020). Temperate phages modify the biochemical pathways between host bacteria and affect communication between infected and uninfected cells. Engineering of the bacterial host genome by prophages has beneficial effects on bacterial cellular processes. Prophages influence the metabolism of host bacteria because they modify the resistance of bacteria to other bacteriophages, the development of bacterial cells, or the production of virulence factors. Once released, these bacteriophages are able to lyse competing strains, genetically and physiologically alter the association between bacteria. In addition, phage-mediated release of intracellular substances such as nutrients to surrounding cells has been described (Barr et al., 2013). Undoubtedly, phages can cause lysis of other bacteria, being harmless to cells lysogenic for the same phage species (Żaczek et al., 2016). Finally, temperate bacteriophages also play an important role in protecting their host from various phage infections (Alcami et al., 2002). It has long been known that the microorganisms that naturally inhabit the digestive system are extremely important for maintaining proper homeostasis and therefore for the normal functioning of the immune system. The diversity of the human microbiota can be controlled by the phages present in the intestinal tract. Based on current viral genome sequencing techniques, it is argued that there is great virion variability among humans, and only a small proportion of intestinal phages is common. Reyes et al. (2010) suggested that temperate bacteriophages make up the majority of enteric viruses (Burcelin, 2016; Park et al., 2014]. However, other results have shown that the concentration of phages may be higher, about 10 10 -10 12 bacteriophage particles per gram of stool. There is evidence that about 82% of adult intestinal bacteria are lysogens, which contain the genetic material of prophages in their genomes (Fortier, 2017). It is also possible to induce prophages from intestinal bacteria under the influence of widely used drugs (Jancheva and Böttcher, 2021). Bifidobacteria bacteriophages influence the diversity and composition of intestinal strains. Maternal bifidophages are able to be transmitted to infants and regulate the composition of the intestinal microbiota of infants (Abeles and Pride, 2014; Lugli et al., 2016). It was found also that the

adhesion of pathogenic bacterial strains to human HT29 cells was reduced after administration of the probiotic lysogenic strains S. thermophilus J34. This suggests that probiotic strains with prophages may have a beneficial effect on the human gastrointestinal tract (Brodin and Davis, 2017; Górski et al., 2006). It is estimated that more than 3% of the bifidobacteria genome consists of bifidoprophages [Górski et al., 2016; Jończyk-Matysiak et al., 2015; Mazaheri Nezhad et al., 2011). This can be beneficial for bacterial strains, but, on the other hand, it can also cause host cell lysis (Górski et al., 2006; Górski et al., 2012). Immediately after birth, the diversity of infant phages remains at a high level, and a week after birth, this correlation tends to decrease (Abeles and Pride, 2014; Pabary et al., 2015). It has been suggested that transmission of maternal bacteriophages occurs through the activation of microbial prophages in milk, vagina, or placental tissue (Jamet et al., 2017; Łobocka et al., 2014; Miernikiewicz et al., 2016). Microscopic analysis of feces and caecum samples showed that in the intestine of an adult, most of the detected phages were derivatives of activated prophages of the families Podoviridae, Siphoviridae, and Myoviridae (Brussow and Hendrix, 2002). Phages can change the microbiological composition in the intestines by reducing the dominant bacteria and allow other strains to develop, creating diverse microbial communities. Thus, phages play an important role in the evolution, diversity, and composition of the human gut microbiota (Thammavongsa et al., 2015). Intestinal phages may have a protective potential, contributing not only to the elimination of bacteria, but also to the regulation of local immune and inflammatory reactions, thereby contributing to the maintenance of immune homeostasis (Alcami et al., 2002; Górski et al., 2015; Relman, 2015). In addition, the phenomenon of translocation may allow phages to migrate to distant tissues and interact with local and distant cells of the immune system. Some phages (for example, T4) can interact with cells of the immune system using the Lys-Gly-Asp sequence present in the gp24 capsid protein and the corresponding β-3 cell receptor integrin, also used by some pathogenic viruses (Abeles and Pride, 2014). Interestingly, this sequence is also present in the CD40 ligand, which is known to activate the endothelium and platelets, promote inflammation, and is critical for T- and B-lymphocyte activation, as interruption of CD40-CD40L interactions has strong immunosuppressive properties. Barr et al., described a symbiotic relationship between a phage and a multicellular host providing antimicrobial protection actively protecting intestinal mucosal surfaces from bacterial invasion (Jończyk-Matysiak et al., 2015). Many authors have observed an increased ratio of phages to bacteria on all studied mucosal surfaces. This enrichment occurs through binding interactions between mucin glycoproteins and the domains of immunoglobulin-like proteins exposed on phage capsids and confer mucosal immunity (Górski and Weber-Dąbrowska, 2005; Górski et al., 2017).

Stimulation and inhibition of phagocytosis

Phagocytosis, one of the types of endocytosis, is an extremely important mechanism of innate immunity that helps Figureht against various pathogens. The whole arsenal of cytostatics directed against bacteria (including both oxygen-dependent and independent mechanisms), after their absorption by phagocytes, causes a number of effects leading to its elimination (Górski et al., 2015). Some drug molecules can be taken in by cells by phagocytosis and can also inhibit this process (Howard-Varona et al., 2017). Therefore, it is important to understand the influence of various factors on endocytic processes. Due to the fact that many bacteria have integrated prophages in their genomes that can detect their presence only under certain conditions, at some point attention began to be paid to the possible effect of these temperate phages on phagocytes and the process of intracellular killing. It has been found that prophages can modulate the human immune response to bacterial infection (Borysowski et al., 2010). Scientists Młynarczyk et al. (1989) described the process of lysogenic conversion, which may affect the susceptibility of a Staphylococcus aureus strain to phagocytosis (Castro-Mejia et al., 2015). The authors investigated the intracellular destruction of non-lysogenic S. aureus strain 8325-4 and its eight lysogenic variants by granulocytes isolated from human blood. After one hour of incubation, the level of intracellular killing was assessed. For lysogenic strains, the level of intracellular killing after an hour ranged from 29–38%, while for a non-lysogenic strain it was 63%. These observations confirmed that the lysogenic staphylococcal strain 8325-4 was less susceptible to intracellular killing by granulocytes compared to the strain without the prophage. It is likely that the observed phenomenon is associated with prophage genes, which may affect the synthesis of antiphagocytic surface receptors or may be the result of the presence of R-plasmids in cells. The authors also investigated the effect of the presence of a prophage in S. aureus.8325-4 on the intensity of leukocyte stimulation using a bioluminescent test. The results showed that the bioluminescence of leukocytes after stimulation with lysogenic strains was lower than that of non-lysogenic strains (Pabary et al., 2015; Ravin, 2015). In addition, other studies have examined the effect of group F prophages on bacterial stimulation of human leukocytes (Bondy-Denomy and Davidson, 2014; Eriksson, 2009; Łusiak-Szelachowska et al., 2017). Leukocyte chemiluminescence for lysogenic S. aureus 8325-4 was at the level of 15.4–37.2% compared to the control strain without prophage (100% bioluminescence). Intracellular leasing of the non-lysogenic strain after 30 and 60 minutes was at the level of 19 and 63%, respectively. For two strains with prophages, after 30 min of incubation with human leukocytes, the level of intracellular killing was very low, and 32–38% of bacteria died after 60 minutes. The decrease in leukocyte stimulation by lysogenic strains may be associated with an increase in the pathogenicity of bacteria that have prophage genes integrated into the genome, compared with strains without prophage. Interestingly,

the Pf prophage genes are very widespread in the genome of Pseudomonas biofilm-forming strains. In addition, the growth of the P. aeruginosa biofilm promotes the production of the Pf phage (Majewska et al., 2015). As shown in a mouse model of pneumonia, P. aeruginosa biofilm formation and production of the Pf prophage inhibit the spread of bacteria from the lungs to other tissues. In addition, these phages contributed to the inhibition of P. aeruginosa during the invasion of airway epithelial cells. This suggests that Pf phage particles can interact with the host bacterium in the lungs. In vivo studies have shown that Pf phages inhibit neutrophil recruitment, reduce cytokine levels, and protect the lungs from damage caused by infection. In addition, the production of Pf phages by bacteria leads to less efficient phagocytosis by macrophages in vivo compared to non-lysogenic strains.

Decreased phagocytosis at the presence of the temperate bacteriophage Pf has been known for a long time and has been described in detail. Pf phages internalized into the endosomes of phagocytic cells activate TLR3 receptors, which leads to stimulation of extracellular secretion of interferons, which in turn inhibit TNF-α secretion. Switching off pro - inflammatory mediators weakens the phagocytosis of pathogenic bacteria.

Role of prophages in biofilm formation.

Biofilm formation has a great impact on the physiology and survival of bacteria, allowing cells to withstand various harmful environmental factors. The biofilm is of great importance in the pathogenicity of many bacteria, including P. aeruginosa, making it extremely difficult to control these bacteria. The role of bacterial biofilm is especially noticeable in the development of diseases such as periodontitis and caries, pneumonia or urinary tract infections. Surprisingly, prophages have been found to play an important role in the production of biofilms by various bacterial species. Bacillus anthraces are unable to form a biofilm when deprived of prophages. The Wip4 prophage encodes the sigma factor of RNA polymerase, which is responsible for activating the expression of genes whose products are necessary for biofilm formation. It was found that the P. aeruginosa cells included in the biofilm most efficiently express the genes present in the genome of the Pf4 prophage.

Extracellular DNA is an essential element of the regular biofilm produced by various bacteria. It has been shown that such DNA appears in a biofilm formed by Streptococcus pneumoniae due to spontaneous induction of the SV1 prophage and lysis of a small proportion of cells initially included in the structure of an immature biofilm. This can be seen as another example of "bacterial altruism" where a small fraction of bacterial cells are sacrificed to make it easier for the rest of the population

to survive. Toll-like receptors (TLRs) are the most studied class of pattern recognition receptors that recognize conserved microbial components called pathogen-associated molecular patterns. Recognition of pathogen-associated molecular patterns by pattern recognition receptors, including TLRs, is essential for the induction of innate immune responses to pathogenic viruses (Górski et al., 2006; Górski et al., 2016). However, while knowledge about the interaction between pathogenic viruses and TLRs is very extensive, data on the effect of phages on TLRs are extremely scarce. There are only two studies that suggest that phage virions can stimulate TLR (Żaczek et al., 2016). In the first study, mice deficient in MyD88, a protein essential for signaling through all TLRs (except TLR3), did not respond to immunization with M13 phage, unlike wild-type mice. However, it must be emphasized that so far no studies have been conducted to evaluate direct interactions between phage particles and individual TLRs. Studies have shown that neither purified T4 phage nor E. coli phage lysate significantly affects the expression of TLR2 and TLR4 on human monocytes (Burke et al., 2001).

Influence of phages to the tumor growth

Over the past two decades, evidence has accumulated to suggest that phages can effectively inhibit tumor growth and metastasis formation. This confirms observations made as early as 1940 indicating that phages have antitumor activity in mice and rabbits. Interestingly, molecular mechanisms similar to those described above may be at least partially responsible for the antimetastatic effects of T4 phage and its HAP1 substrain against melanoma cells in mouse experimental cancer models. In addition, using various mouse models, it was noted that oral administration of phage was more effective than intraperitoneal administration of phage: 3% inhibition of metastases was noted with intraperitoneal administration of purified T-phage compared to 29% inhibition with oral administration; these values were 19 and 80%, respectively, for the purified HAP1 phage. Another anticancer effect of phages may depend on their ability to enhance the antitumor response initiated by vaccines based on dendritic cells (Łobocka et al., 2014; Soto, 2014).

Influence of the phages to the virulence factors.

Van Wamel et al. (2006) used 5 classical laboratory and 85 clinical strains of S. aureus to study the distribution of temperate βC-ϕs phages (Bae et al., 2006). Their results showed that βC-ϕs were present in 88.9% of the staphylococcal strains analyzed. The presence of various virulence factors encoded by them is also

described. SAK (staphylokinase), CHIPS (chemotaxis inhibiting protein) and two superantigens SEA and SEP were found in 76.6, 56.6, 27.8 and 7.8% of the strains, respectively. The aforementioned modulators of the human innate immune system can be easily and efficiently transferred by β-hemolysin (βC-ϕs) converting phages between staphylococcal strains (Jamet et al., 2017). CHİPS (encoded by the chp gene) is a protein that has a stronger inhibition of calcium mobilization induced by complement protein C5a. Consequently, the activation of phages in response to formylated peptides and C5a, as well as the chemotaxis of human neutrophils, is inhibited. CHIPS as a virulence factor of S. aureus strains protects bacteria from the innate immune system (Soto, 2014; Thammavongsa et al., 2015). SAK (staphylococcal antigen) affects the innate immune system in various ways, for example by inhibiting opsonization (Żaczek et al., 2016). Staphylococcal superantigens have the ability to directly bind to MHC class II molecules, which can lead to the activation of monocytes and, consequently, their stimulation to increase the secretion of chemokines and other pro-inflammatory cytokines (Żaczek et al., 2016).

Panton-Valentine leukocidin is a factor that significantly increases the pathogenicity of MRSA strains. Depending on the concentration, PVL causes necrosis or apoptosis of human cells in vitro due to the formation of pores in cells or their organelles, such as mitochondria. About 30% of the isolated strains are PVL-positive, which is associated with the presence of prophage genes in their genome. Interestingly, it was shown that the distribution of individual phages carrying the PVL toxin gene depended on the geographic location from which the bacterial strain was obtained. PVL induces an anti-inflammatory response by binding to monocytes and macrophages, resulting in the release of caspase-1 dependent cytokines (IL-18 and IL-1β). The cytotoxic effect on neutrophils also causes the release of PAMP (pathogen-associated molecular patterns) and DAMP (damage-associated molecular patterns) particles from them and, consequently, an increase in the level of pro-IL-1β in monocytes and macrophages. However, there are also conflicting data on that PVL at the appropriate concentration may have a protective effect and increase the ability of the immune system to Figureht against staph infections. As can be seen, the genes carried by prophages significantly modulate the immune response.

Conclusion

• Phages are present in high concentrations in the intestinal tract, where they can interact not only with bacteria, but also with intestinal lymphoid tissue cells.

• Phages can interact with cells of the immune system through their proteins and cell receptors. Some of these receptors belong to the β-integrin family.

• Phage interactions with immune cells appear to have an immunomodulatory effect, suppressing elevated responses both in vitro and in vivo without causing immune deficiency.

References

Abeles SR, Pride DT. (2014). Molecular bases and role of viruses in the human microbiome. J. Mol. Biol. 426 (23), 3892–3906. An article presenting what is currently known about the presence of viruses in the human microbiome.

Alcami A, Ghazal P, Yewdell JW. (2002). Viruses in control of the immune system. Workshop on molecular mechanisms of immune modulation: lessons from viruses. EMBO Rep. 3(10), 927–932.

Bae T., Baba T., Hiramatsu K., Schneewind O. (2006). Prophages of Staphylococcus aureus Newman and their contribution to virulence. Mol. Microbiol. 62:1035–1047.

Barr JJ, Auro R, Furlan M. (2013). Bacteriophage adhering to mucus provide a non-host-derived immunity. Proc. Natl Acad. Sci. USA, 110 (26): 10771–10776.

Bloch H. (1940). Experimental studies on the relationship between bacteriophages and malignant tumors. Archive for all virus research. 1(4): 481-496. Bondy-Denomy J., Davidson A.R. (2014). When a virus is not a parasite: The beneficial effects of prophages on bacterial fitness. J. Microbiol. 52:235–242.

Borysowski J, Wierzbicki P, Kłosowska D, Korczak-Kowalska G, Weber-Dąbrowska B, Górski A. (2010). The effects of T4 and A3/R phage preparations on whole-blood monocyte and neutrophil respiratory burst. Viral Immunol. 23(5): 541–544.

Brodin P, Davis MM. (2017). Human immune system variation. Nat. Rev. Immunol. 17(1), 21–29. Summary of current knowledge on how the bacterial microbiota affects the immune system.

Brussow H., Hendrix R.W. (2002). Phage genomics: Small is beautiful. Cell. 108:13–16.

Bruttin A, Brüssow H. (2005). Human volunteers receiving Escherichia coli phage T4 orally: a safety test of phage therapy. Antimicrob. Agents Chemother. 49(7): 2874–2878.

Burcelin R. (2016). Gut microbiota and immune crosstalk in metabolic disease. Mol. Metab. 5(9): 771–781.

Burke J., Schneider D., Westpheling J. (2001). Generalized transduction in Streptomyces coelicolor. Proc. Natl. Acad. Sci. USA. 98:6289–6294.

Castro-Mejia J.L., Muhammed M.K., Kot W., Neve H., Franz C.M., Hansen L.H., Vogensen F.K., Nielsen D.S. (2015). Optimizing protocols for extraction of bacteriophages prior to metagenomic analyses of phage communities in the human gut. Microbiome. 3:64.

Dąbrowska K, Miernikiewicz P, Piotrowicz A et al. (2014). Immunogenicity studies of proteins forming the T4 phage head surface. J. Virol. 88 (21): 12551–12557.

Dąbrowska K, Opolski A, Wietrzyk J et al. Activity of bacteriophages in murine tumor models depends on the route of phage administration. Oncol. Res. 15(4): 183–187.

Erez Z., Steinberger-Levy I., Shamir M., Doron S., Stokar-Avihail A., Peleg Y., Melamed S., Leavitt A., Savidor A., Albeck S., et al. (2017). Communication between viruses guides lysis-lysogeny decisions. Nature. 541:488–493.

Eriksson F, Tsagozis P, Lundberg K et al. (2009). Tumor-specific bacteriophages induce tumor destruction through activation of tumor-associated macrophages. J. Immunol. 182(5): 3105–3111.

Fortier L.C. (2017). The Contribution of Bacteriophages to the Biology and Virulence of Pathogenic Clostridia. Adv. Appl. Microbiol. 101:169–200.

Garrett WS. (2017). Gut microbiota in 2016: a banner year for gut microbiota research. Nat. Rev. Gastroenterol. Hepatol. 14(2): 78–80.

Górski A, Dąbrowska K, Hodyra-Stefaniak K, Borysowski J, Międzybrodzki R, Weber-Dąbrowska B. (2015). Phages targeting infected tissues: novel approach to phage therapy. Future Microbiol. 10(2): 199–204.

Górski A, Kniotek M, Perkowska-Ptasińska A et al. (2006). Bacteriophages and transplantation tolerance. Transplant. Proc. 38(1): 331–333.

Górski A, Międzybrodzki R, Borysowski J et al. (2012). Phage as a modulator of immune responses: practical implications for phage therapy. Adv. Virus Res. 83: 41–71.

Górski A, Międzybrodzki R, Weber-Dąbrowska B. (2016). Phage therapy: combating infections with potential for evolving from merely a treatment for complications to targeting diseases. Front. Microbiol. 7: 1515

Górski A, Ważna E, Weber-Dąbrowska B, Dąbrowska K, Świtała-Jeleń K, Międzybrodzki R. (2006). Bacteriophage translocation. FEMS Immunol. Med. Microbiol. 46(3): 313–319.

Górski A, Weber-Dąbrowska B. (2005). The potential role of endogenous bacteriophages in controlling invading pathogens. Cell. Mol. Life Sci. 62(5): 511–519.

Górski A., Dąbrowska K., Międzybrodzki R., Weber-Dąbrowska B., Łusiak-Szelachowska M., Jończyk-Matysiak E., Borysowski J. (2017). Phages and immunomodulation. Future Microbiol. 12: 905–914.

Howard-Varona C., Hargreaves K.R., Abedon S.T., Sullivan M.B. (2017). Lysogeny in nature: Mechanisms, impact and ecology of temperate phages. ISME J. 11:1511–1520.

Hargreaves K.R., Kropinski A.M., Clokie M.R. (2014). Bacteriophage behavioral ecology: How phages alter their bacterial host's habits. Bacteriophage. 4:e29866.

Jamet A., Touchon M., Ribeiro-Goncalves B., Carrico J.A., Charbit A., Nassif X., Ramirez M., Rocha E.P.C. (2017). A widespread family of polymorphic toxins encoded by temperate phages. BMC Biol. 15:75.

Jancheva M., Böttcher T. (2021). A Metabolite of Pseudomonas Triggers Prophage-Selective Lysogenic to Lytic Conversion in Staphylococcus aureus. J. Am. Chem. Soc.

Jain L, Rawat M, Ramakrishnan S, Kumar B. (2017). Active immunization with Brucella abortus S19 phage lysate elicits serum IgG that protects guinea pigs against virulent B. abortus and protects mice by passive immunization. Biologicals 45: 27–32.

Jończyk-Matysiak E. (2015). Ph.D. Thesis. Ludwik Hirszfeld Institute of Immunology and Experimental Therapy Polish Academy of Sciences; Wrocław, Poland: The Effect of Bacteriophage Preparations on Intracellular Killing of Bacteria by Phagocytes.

Jończyk-Matysiak E., Łusiak-Szelachowska M., Kłak M., Bubak B., Międzybrodzki R., Weber-Dąbrowska B., Żaczek M., Fortuna W., Rogóż P., Letkiewicz S., et al. (2015). The Effect of Bacteriophage Preparations on Intracellular Killing of Bacteria by Phagocytes. J. Immunol. Res. 2015:482863.

Kazmi S.U., Kansal R., Aziz R.K., Hooshdaran M., Norrby-Teglund A., Low D.E., Halim A.-B., Kotb M. (2001). Reciprocal, temporal expression of SpeA and SpeB by invasive M1T1 group a streptococcal isolates in vivo. Infect. Immun. 69:4988–4995.

Kim KP, Cha JD, Jang EH et al. (2008). PEGylation of bacteriophages increases blood circulation time and reduces T-helper type 1 immune response. Microb. Biotechnol. 1(3), 247–257.

Lasserre J.F., Brecx M.C., Toma S. (2018). Oral Microbes, Biofilms and Their Role in Periodontal and Peri-Implant Diseases. Materials. 11:1802.

Łobocka M., Hejnowicz M.S., Gągała U., Weber-Dąbrowska B., Węgrzyn G., Dadlez M. (2014). The first step to bacteriophage therapy—How to choose the correct phage. In: Borysowski J., Międzybrodzki R., Górski A., editors. Phage Therapy: Current Research and Applications. Caister Academic Press; Norfolk, UK: 23–69.

Lugli G.A., Milani C., Turroni F., Tremblay D., Ferrario C., Mancabelli L., Duranti S., Ward D.V., Ossiprandi M.C., Moineau S., et al. (2016). Prophages of the genus Bifidobacterium as modulating agents of the infant gut microbiota. Environ. Microbiol. 18:2196–2213.

Łusiak-Szelachowska M, Żaczek M, Weber-Dąbrowska B et al. (2017). Antiphage activity of sera during phage therapy in relations to its outcome. Future Microbiol. 12(2): 109–117.

Mai-Prochnow A., Hui J.G., Kjelleberg S., Rakonjac J., McDougald D., Rice S.A. (2015). Big things in small packages: The genetics of filamentous phage and effects on fitness of their host. FEMS Microbiol. Rev. 39:465–487.

Majewska J, Beta W, Lecion D et al. (2015). Oral application of T4 phage induces weak antibody production in the gut and in the blood. Viruses 7(8), 4783–4799.

Mazaheri Nezhad Fard R., Barton M.D., Heuzenroeder M.W. (2011). Bacteriophage-mediated transduction of antibiotic resistance in enterococci. Lett. Appl. Microbiol. 52:559–564.

Miernikiewicz P, Kłopot A, Soluch R et al. (2016). T4 phage tail adhesin gp12 counteracts LPS-induced inflammation in vivo. Front. Microbiol. 7, 1112.

Pabary R, Singh C, Morales S et al. (2015). Antipseudomonal bacteriophage reduces infective burden and inflammatory response in murine lung. Antimicrob. Agents Chemother. 60(2), 744–751.

Park K, Cha KE, Myung H. (2014). Observation of inflammatory responses in mice orally fed with bacteriophage T7. J. Appl. Microbiol. 117(3), 627–633.

Ravin N.V. (2015). Replication and Maintenance of Linear Phage-Plasmid N15. Microbiol. Spectr. 2:3:PLAS-0032.

Relman D. (2015). The human microbiome and the future practice of medicine. JAMA 314(11), 1127–1128.

Sausset R., Petit M.A., Gaboriau-Routhiau V., De Paepe M. (2020). New insights into intestinal phages. Mucosal. Immunol. 13:205–215.

Soto S.M. (2014). Importance of Biofilms in Urinary Tract Infections: New Therapeutic Approaches. Adv. Biol. 543974:13.

Thammavongsa V, Kim HK, Missiakas D, Schneewind O. (2015). Staphylococcal manipulation of host immune responses. Nat. Rev. Microbiol. 13(9), 529–543.

Żaczek M, Łusiak-Szelachowska M, Jończyk-Matysiak E et al. (2016). Antibody production in response to staphylococcal MS-1 phage cocktail in patients undergoing phage therapy. Front. Microbiol. 7, 1681.