ALTERNATIVES TO ANTIBIOTICS: PHAGE LYTIC ENZYMES AND PHAGE THERAPY

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Multiple drug resistance of nosocomial bacterial strains provoked by the unwise and uncontrolled use of antibiotics in medicine and agriculture seriously threatens modern healthcare: minor and trivial infections are about to kill again. A solution may lie in the development of new alternatives to antibiotics. This review highlights the most interesting approaches to the development of antibacterial drugs focusing on the most promising ones, such as phage therapy and phage lytic enzymes (lysins).

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АЛЬТЕРНАТИВЫ АНТИБИОТИКАМ: ЛИТИЧЕСКИЕ ФЕРМЕНТЫ БАКТЕРИОФАГОВ И ФАГОВАЯ ТЕРАПИЯ

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Множественная лекарственная устойчивость госпитальных штаммов бактерий, возникшая в результате неразумного неконтролируемого применения антибиотиков в медицине и сельском хозяйстве, представляет одну из серьезнейших угроз для современного здравохранения: привычные инфекции вновь могут убивать, как раньше. Решение проблемы может быть найдено в процессе разработки альтернатив антибиотикам. В обзоре приведены краткие сведения о наиболее интересных подходах к созданию новых антибактериальных средств и подробно проанализированы наиболее преспективные из них, такие как фаговая терапия и литические ферменты бактериофагов (фаголизины).

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The antibiotic era: from victory to defeat

Back in the early 19th century an opinion prevailed that disease is caused by imbalances in the body. It was only in the mid-century that Louis Pasteur linked infections to their causative agents, germs. The day in 1928 when penicillin was discovered by the British bacteriologist Alexander Fleming became a milestone in the history of medicine, marking the advent of the antibiotic era. Antibiotics were initially seen as a universal remedy, a super weapon capable of turning the tide in the war against infectious diseases. But the euphoria did not last long. As our knowledge accumulated, more new antibiotics were discovered with various mechanisms of action, different properties and spectra of activity; but bacteria struck back by developing resistance to those drugs, frustrating the efforts of researchers and doctors [1]. So hopes were pinned on last-resort antibiotics, such as colistin and daptomycin.

In May 2015 the World Health Organization (WHO) admitted that bacterial resistance to antibiotics was the underlying cause of the ongoing healthcare crisis and proposed the Global Action Plan on Antimicrobial Resistance [2]. However, it was only a few months after that a mobile colistin-resistance gene was discovered in November 2015 [3]. A similar report followed in October 2016 describing a daptomycin-resistant *Staphilococcus aureus* strain capable of inactivating the antibiotic by releasing membrane phospholipids into the surrounding environment once they have bound daptomycin [4]. In September 2016, a month before that report, an

American patient died of sepsis caused by the gram-negative "superbacteria" *Klebsiella pneumoniae* resistant to all 26 antibiotics approved in the US [5]. The analysis of all known antibiotics and their therapeutic combinations published by WHO in 2017 [6] uncovered a sad truth: there is currently no cure for infections caused by gram-negative multidrug-resistant bacteria. Last-resort antibiotics, the defense we thought reliable, no longer work, and trivial infections can kill once again. This urges us to develop novel antibiotics or start searching for an alternative that will be just as effective.

Sources for new antibiotics

Antibiotics are natural, synthetic or semisynthetic chemicals whose small concentrations are capable of inhibiting microbial growth. The primary source of clinically important antibiotics is actinomycetes and sometimes non-mycelial bacteria, so these microorganisms may still have something new to offer. Another way to discover a novel antibiotic is a screening for a candidate chemical structure and predicting its orientation and position in the active site of a target protein.

That said, the search for novel antibiotics has almost stopped, and for a few understandable reasons. First, most antibiotics target one of three key prokaryotic metabolic pathways and processes, including protein biosynthesis, DNA replication and bacterial cell wall synthesis [7]. The majority of possible approaches to these targets have already been proposed and scrutinized. Besides, there is always a risk of spontaneous mutations in bacteria that can ruin years of efforts spent in a scientific lab and incur additional costs. Second, to discover a single antibiotic, one has to analyze about a million new actinomycetes [8], which is a very costly procedure.

Over 90 % of all bacterial species found in the environment cannot be cultured in a lab under standard conditions [9]. However, recently it has become possible to create specific conditions favorable for such bacteria in order to identify producers of yet unknown antibiotics among those species. This gave rise to two conceptually different search strategies: screening for a source of new antibiotics among unculturable bacteria and production of novel synthetic antibiotics. Both strategies are starting to pay off. For example, screening of uncultured soil bacteria has revealed a previously unknown antibiotic (teixobactin) that kills gram-positive bacteria [10]. Another antibiotic PEG-2S that inhibits Na^+ translocating NADH:ubiquinone oxidoreductase has been synthesized in the lab [11].

Of particular interest are synthetic antibiotics targeting bacterial bioenergetics [12]. In 2012, the Food and Drug Administration (USFDA) approved bedaquiline synthesized after 4 decades of research for the treatment of tuberculosis. This drug targets mycobacterial ATP synthase suppressing bacterial bioenergetics, which is causing death for the affected cells [13].

Based on the symbiotic theory a supposition was made that antioxidants that induce collapse of mitochondrial membrane potential can be effective against bacteria. Lately it has been found that the antioxidant SkQ1, a synthetic triphenyl phosphonium-based compound, can kill bacteria by decreasing their membrane potential [14, 15].

Alternatives to antibiotics

In spite of the astonishing variety of approaches to the discovery of effective alternatives to antibiotics and more than ten years of painstaking research, there have been no serious breakthroughs in the therapy of infections. Few candidate substitutes seem to work.

Among the most interesting alternatives to antibiotics are vaccines, antibodies, probiotics, immunostimulants, photosensitizers, natural bacteriophages, phage lytic enzymes, synthetic bacteriophages, antimicrobial peptides, host-defense peptides, antibiofilm compounds, multidrug efflux pump inhibitors, immunosuppressants, liposome entrapment of toxins, metal chelators, antibacterial nucleic acids, anti-resistance nucleic acids, and antibacterial peptides. This list is not exhaustive, though.

Based on the evaluation of clinical potential and relative simplicity of use, a conclusion can be drawn that phage lysins and multidrug efflux pump inhibitors are the most promising therapeutic alternatives to antibiotics, while vaccines and antibodies seem to have a good potential as prevention tools, and probiotics can be used for both treatment and disease prevention. Bacteriophages, antibiofilm compounds, antimicrobial peptides and photosensitizers also hold promise; however, it is not clear yet whether they can enter the market as finished pharmaceutical products to replace existing antibiotics. There are also doubts about immunostimulants that are sometimes used for disease prevention or as complementary drugs: their clinical significance is yet to be elucidated; therefore, they do not seem to be an adequate substitute for antibiotics.

Many of the approaches listed above are either undergoing experimental trials or exist as theories. More information about them can be found in the review [16] ordered by the Wellcome Trust foundation (UK) and prepared by the researchers from academic circles and the pharmaceutical industry. In this article we focus on the most promising and interesting alternatives to antibiotics, including vaccines, antibodies, multidrug efflux pump inhibitors, photosensitizers, bacteriophages and phage lysins.

Vaccines

Vaccines are a well-established and effective method of disease prevention. In 2015 the novel multicomponent vaccine Bexsero (GlaxoSmithKline Biologicals, UK) against *Neisseria meningitidis* was introduced into the national infant immunization program in the UK. *Neisseria meningitidis* is the causative agent of pediatric meningitis and bacteriaemia. Because its capsular polysaccharide MenB, which is a virulence factor, resembles human cell adhesion molecules, effective induction of antibodies against meningococcal infection is a difficult task. A group of British researchers managed to solve it by conducting a bioinformatic search for a candidate antigen. The antigen contained in the outer membrane vesicles was later shown to elicit sustained immune response upon vaccination. The approach used by the British researchers is referred to as reverse vaccinology. Bexsero is effective against 73 % to 88 % of group B meningococcal strains (MenB) [17]. That said, it is still very unlikely that antibiotics will be fully replaced by such vaccines in the nearest future.

Antibodies

A wide range of unique properties makes antibodies a keystone of contemporary medicine. Pathogen-specific monoclonal antibodies are either used independently for disease prevention or in combination with antibiotics to treat bacterial infections [18]. Antibodies neutralize the effects of bacterial toxins [19–22]; they can also be directed against bacterial antigens [23–25] and quorum-sensing signals [26, 27]. Together, traditional antibiotics and antibodies open new possibilities for

inhibiting biofilm formation enhancing the effect of antibiotic–based treatment and can be employed for combating persister cells insensitive to antibiotics [28, 29].

Multidrug efflux pump inhibitors

Although these compounds were known before, they are now receiving closer attention [30, 31] owing to the peculiar interactions between the substrates of multidrug efflux pumps and their inhibitors [15, 32]. Efflux pump inhibitors are a conceptually new approach to fighting bacteria not mentioned in the review [16], helping to reduce therapeutic concentrations of antibiotics administered to a patient by an order of magnitude or two. This phenomenon was first demonstrated using a novel antibiotic SkQ1, with pump inactivation leading to a 50-fold reduction in its minimum inhibitory concentrations. The bad news is that normally several pumps are involved in pumping antibiotics out, and the inhibitors often affect a multitude of different pumps simultaneously. Importantly, SkQ1 is recognized only by the main multidrug efflux pump of *Escherichia coli*, AcrAB-TolC [15]. Indeed, the use of efflux pump inhibitors provides a solution to the problem of antibiotic resistance.

Photosensitizers

Antimicrobial photodynamic therapy or inactivation (aPDT or aPDI) is new effective method of killing gram-negative and gram-positive bacteria and yeast [33–36]. aPDI employs a non-thermal reaction induced by the interactions between visible light photons and a photosensitizer, such as methylene blue, chlorin, porphyrin, chlorophyll or their derivatives, in the presence of oxygen. Reactive oxygen species produced as shown in Fig. 1 effectively kill bacterial cells, including *Pseudomonas aeruginosa*. This therapy is in particular demand in dentistry and dermatology [36] where it can replace local antibiotic treatment.

Phage therapy

Bacterial viruses or bacteriophages constitute the largest group of viruses with double-stranded genomic DNA, although there are phages with single stranded DNA and single/double-stranded RNA [37]. In total, the number of phages is estimated to be as high as 10^{31}–10^{32} [38]. They play an important role in the regulation of the world's bacterial population. Phages kill 20–40 % of sea bacteria per day [39]. The use of phages as therapeutic agents was proposed and successfully tested by Twort [40], D'Herelle [41], Bruynoghe and Maisin [42] in the early 20th century. However, phages did not become a popular treatment option at that time largely because antibiotics kept gaining ground and there was a lack of theoretical knowledge to explain phages' failure in clinical trials [43].

According to the contemporary views, phages used for treating bacterial infections must meet a few requirements: 1) they have to be lytic; 2) their therapeutic concentrations must be calculated for each particular infection; 3) a phage receptor involved must be well studied; 4) the final formulation must be free of bacteria and 5) contain viable bacteriophage particles [44–46]. The positive effect of phage therapy, i.e. reduction in the pathogen count down to the level at which the organism can handle the infection on its own [47], varies between individuals depending at the same time on a few other factors, which prevents phages from entering American and European markets [46].

Both bacteriophages and antibiotics directly attack bacteria; therefore, their effectiveness can be compared. Advantageously, bacteriophages are more specific for certain bacterial strains, such as *Clostridium difficile* that causes intestinal infections or diarrhea following antibiotic treatment [48]. Also, phage therapy is more sparing than antibiotic-based therapies [49, 50]. However, if infection is caused by multiple different bacteria, as is the case with wounds, bacteriophages are far less effective than antibiotics [51].

In the experiment [52] *E. coli* were infected with bacteriophages collected in two geographically distant regions: Mexica and Bangladesh. The tested phages turned to be highly specific for bacteria from their home region [52]. However, no significant differences were observed in the outcome of two different treatments (with a Russian bacteriophage cocktail and a placebo) applied to the cohort of 160 Bangladeshi children with *E. coli*-associated diarrhea [53]. Bacteriophages directed against antibiotic-resistant bacterial strains are easier to find in those regions where these bacteria are indigenous [54], which
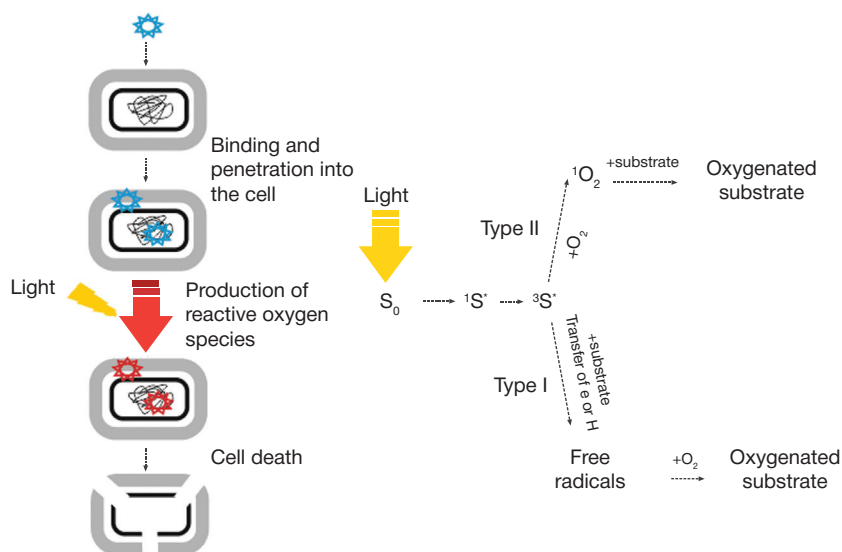
Fig. 1. Schematic illustration of antibacterial photodynamic therapy (left). Photodynamic effects explained on the molecular level (right). Upon absorbing a photon, a photosensitizer molecule (S_0) enters a short-lived excited singlet state ($^1S^*$), moving then to a triplet state ($^3S^*$). After that, two scenarios are possible: either $^3S^*$ reacts with the substrate and intermittent radicals are produced that damage cell structures and macromolecules inside the cell (type I), or energy from $^3S^*$ is transferred to oxygen, and reactive singlet oxygen $^1O_2$ is produced that also damages cell structures or its macromolecules

provides a new insight into the problem of antibiotic resistance and the use of phage therapy.

An idea to use bacteriophages for treating infections caused by biofilm-forming bacteria seems quite attractive. Antibiotics are not the best option here: they inhibit biofilm formation only when administered in high toxic doses [55]. Experiments *in vitro* have demonstrated that bacteriophages prevent formation of biofilms and even destroy them, especially in the case of *Listeria monocytogenes*, *P. aeruginosa* and *Staphylococcus epidermidis* [56, 57].

To predict possible complications or adverse effects of phage therapy, one should be aware of all nuances of phage biology and genome since many phages contain genes coding for virulence factors or toxins [58] or conferring resistance to antibiotics [59–62]. Phage therapy is difficult and requires more caution than antibiotic treatment because of the phenomena of phage-associated botulinum toxins [59], diphtheria toxins [58], cholera toxins [63], and phage-triggered conversion of non-toxic bacteria into toxic [64]. It is believed that life cycles of bacteriophages (Fig. 2) can vary from lytic to lysogenic, including pseudo lysogenic and defective [65, 66]. The genomic analysis of the gigantic bacteriophage *P. aeruginosa* [67–69] has demonstrated that its gene products very much resemble proteins with yet uncharacterized function produced by other organisms.

To sum up, complicated life cycles, a risk of conversion and resistance gene transfer and the variability of phages, as well as mutations in the bacterial population, render phage therapy somewhat unreliable and unpopular, in spite of its good clinical potential.

Phage lytic enzymes (phage lysins)

A bacterial cell envelope is a barrier in the way of bacteriophage DNA that enters the cell in order to infect it or is released back into the surrounding environment as a viral particle. The cell envelope is a complex organized system of lipid and peptidoglycan layers protecting the cell from the invasion of foreign agents. The cell envelope of gram-negative bacteria has three components, including the inner plasma membrane, peptidoglycans and the outer membrane [70, 71], while the cell envelope of gram-positive microorganisms consists of only two components and misses the outer membrane.

The hardest to penetrate is the peptidoglycan layer built from alternating residues of N-acetylglucosamine and N-acetylmuramic acid linked by β-1,4-glycosidic bonds and short peptide chains. Linked together, peptidoglycan blocks (referred to as murein) form a gigantic macromolecule that ensures mechanical stability of the layer and its impermeability to viruses and toxic factors with big molecular weight [37, 70, 71]. Therefore, to get inside the cell, the phage has to locally disrupt the integrity of cell membranes and the peptidoglycan layer. This is done by lytic enzymes called bacteriophage lysins (phage lysins, endolysins or virolysins).

Importantly, the peptidoglycan layer of an infected cell is lysed in a two-step process [72] which includes "lysis from without" followed by phage DNA passage into the cell and "lysis from within" facilitating release of new phage particles into the environment. Normally, the first type of lysis is performed by a capsid-associated phage lysin, such as the gp5 baseplate protein produced by the T4 bacteriophage; this lysin has a functional domain with lytic properties [73, 74]. "Lysis from without" is limited to a particular site on the membrane and lasts just enough time for phage DNA to enter the cell and not be killed by the phage. "Lysis from within" is usually performed by

a soluble phage lysin and is not site-restricted but very limited in time. It follows the massive synthesis of phage lysins in the cell and is activated in parallel with holin integration into the cell membrane. Holin is a regulatory protein that forms nonselective pores in the bacterial membrane. These pores disrupt bacterial metabolism and make the peptidoglycan layer vulnerable to phage lysins, which results in the total lysis of the layer, cell damage and release of phage particles into the environment [75–77].

Soluble phage lysins triggering massive "lysis from within" are interesting candidate alternatives to antibiotics: they can effectively lyse peptidoglycan and, unlike phages, do not depend on holin presence.

There are a few classifications of phage lysins [78–85], including the one based on the mechanism of their action: 1) lysozymes, which hydrolyze β-1,4-bonds between the residues of N-acetylmuramic acid and N-acetylglucosamine in the peptidoglycan molecule; they are subdivided into muramidases and lytic transglycosylases; 2) N-acetylmuramoyl-L-alanine amidases, which hydrolyze the amide bond between N-acetylmuramic acid and L-alanine; 3) peptidases, which hydrolyze the peptide bond between peptidoglycan amino acids, and 4) esterases (Fig. 3).

A study of autolytic enzymes of *S. pneumoniae* revealed that phage lysins have a modular structure, with one domain recognizing the site of lysis and the other cleaving peptidoglycan [86]. The modular structure appeared to be typical for both previously discovered and new phage lysins [87–89], which was later confirmed by genetic engineering experiments involving rearrangement and combination of functional domains [90].

Of course, not all phage lysins have equal potential to become therapeutic agents but some of their properties, such as the ability of PlySs2 to retain its function after 10 hours of freezing and thawing cycles [91] and the ability of PlyG to attack endospores of *Bacillus anthracis* [92], make phage lysins an interesting object for research. They are also species-specific, i. e. they kill only those bacterial (sub)species that are targeted by their phages [93, 94].
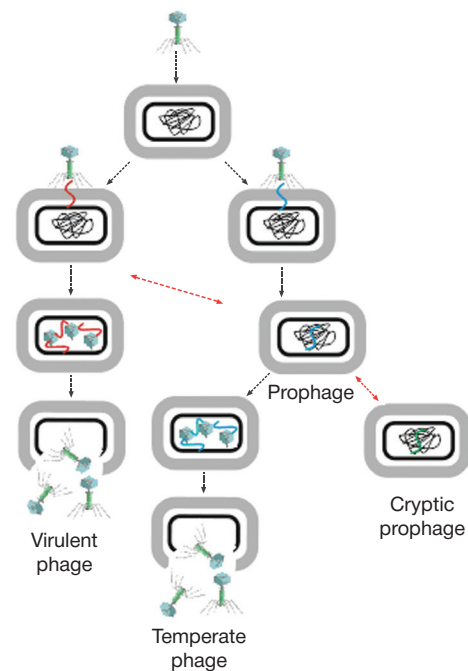

Fig. 2. Possible scenarios of phage infection in the bacterial population. Reversible stages are shown in red (mutations, premature sequence termination in prophages, deletions, insertions, etc.)

Considering the modular structure of natural phage lysins, through simple genetic modifications researchers managed to design chimeric phage lysins for treating complex bacterial infections caused by methicillin-resistant *S. aureus* (MRSA) [95]. Also, combined with low molecular weight antibiotics, such as penicillin or gentamycin, phage lysin Cpl-1 can totally eliminate penicillin–resistant pneumococci [96].

However, the absence of phage machinery facilitating passage through the bacterial cell wall restricts the use of phage lysins. The outer membrane of gram-negative bacteria reduces the therapeutic effect of phage lysins almost to nothing [94]. However, they do work in gram-positive bacteria. In addition, there is a risk of antibody production in response to phage lysins, which may interfere with phage lysin "mission". Both *in vitro* and *in vivo* experiments demonstrate that antibodies impede but not totally block lysis of bacterial cells by phage

lysins [97], which may be explained by the fact that the affinity of the latter to their substrates is possibly higher than the affinity of a generated antibody to the enzyme.

CONCLUSION

Although there are a lot of promising alternatives to antibiotics, none of them seems to be a perfect substitute for antimicrobial drugs. All of them are not so safe, predictable, controllable, easy to use or effective. Still, it is obvious that development of alternative approaches to treating bacterial infections is a vital necessity for today's healthcare. Combination therapies will probably win over others due to the synergistic effect of their components: antibiotics and their alternatives working together.
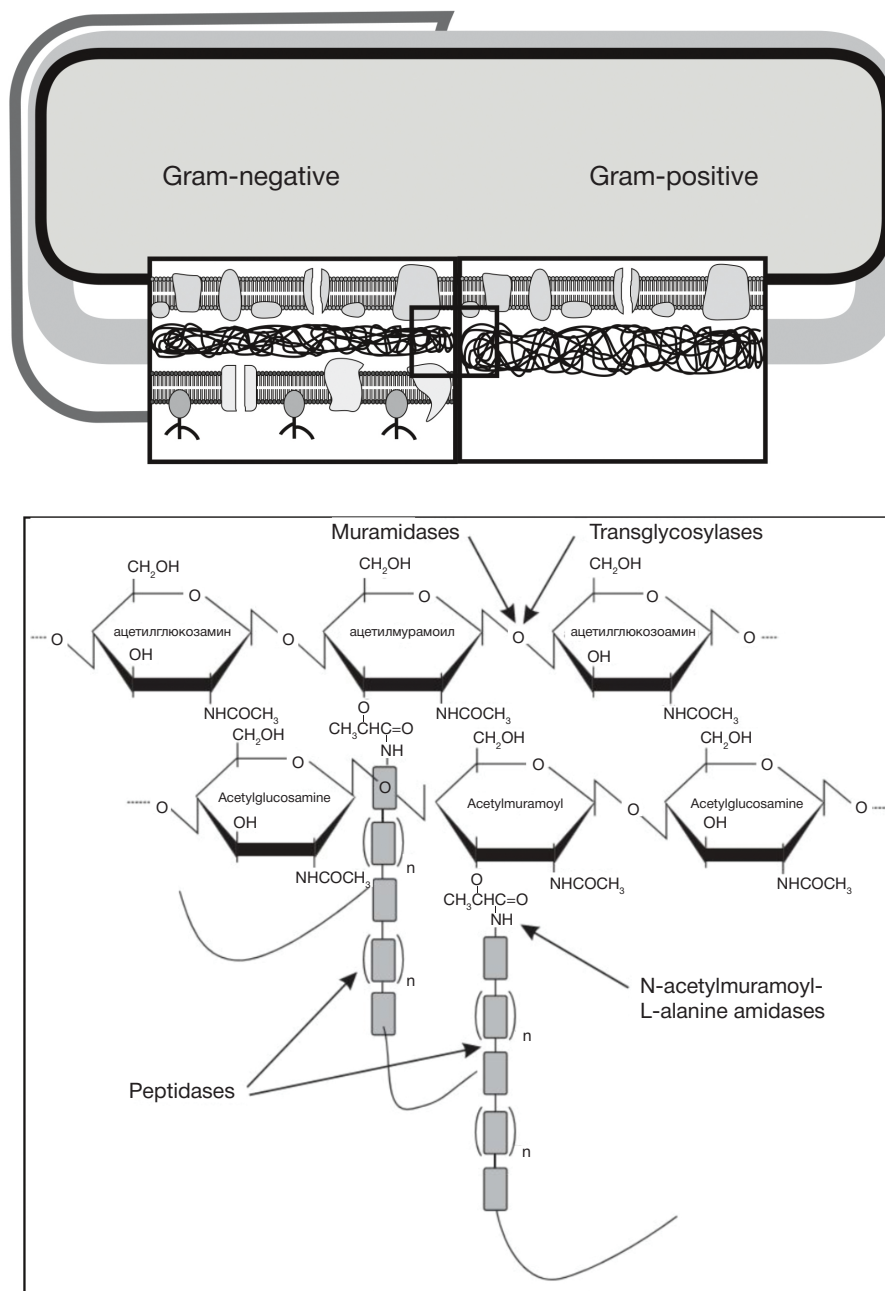

Fig. 3. Schematic of bacterial cell envelopes and phage lysin classes that degrade the peptidoglycan layer

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