TRIPHENYL PHOSPHONIUM-BASED SUBSTANCES ARE ALTERNATIVES TO COMMON ANTIBIOTICS

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There is an urgent need for new antimicrobial and therapeutic strategies to deal with the ever evolving antimicrobial resistance among the most prevalent bacterial pathogens. Infections due to virulent bacteria remain significant causes of morbidity and mortality despite progress in antimicrobial therapy, primarily because of the increasing of antimicrobial resistance levels among such group of bacteria. Despite significant advances in the understanding of the pathogenesis of infection due to these organisms, there are only limited strategies to prevent infection. Recently it was reported that SkQ1, triphenyl phosphonium-based mitochondria-targeted antioxidant and antibiotic, effectively kills all tested Gram-positive laboratory strains including of *Bacillus subtilis*, *Staphylococcus aureus* and *Mycobacterium sp*. Moreover, SkQ1 demonstrated effectiveness towards Gram-negative strains too, except *Escherichia coli*. The mechanism of the bactericidal action of TPP-based antibiotics could be also described by its ability to suppress bacterial bioenergetics by collapsing membrane potential through activation of protonophorous uncoupling. To this date, there are no reports of resistance to SkQ1 among Gram-positive strains; therefore, triphenyl phosphonium-based antibacterial agents would be effective towards planktonic and sessile cells of clinical resistant strains.

ПРОИЗВОДНЫЕ ТРИФЕНИЛФОСФОНИЯ КАК АЛЬТЕРНАТИВА ОБЫЧНЫМ АНТИБИОТИКАМ

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В связи с тем, что наиболее распространенные патогены постоянно эволюционируют, приобретая устойчивость ко все большему числу антибиотиков, в настоящее время существует острая потребность в новых антимикробных препаратах и стратегиях лечения инфекций, вызываемых антибиотикорезистентными бактериями. Хотя в понимании патогенеза подобных инфекций удалось значительно продвинуться, стратегий для борьбы с ними не так много. Недавно было показано, что SkQ1, антиоксидант и антибиотик на основе трифенилфосфония, воздействующий на митохондрии, эффективен в отношении грамположительных лабораторных штаммов, включая *Bacillus subtilis*, *Staphylococcus aureus* и *Mycobacterium sp*. Более того, SkQ1 также показал эффективность в отношении грамотрицательных штаммов за исключением *Escherichia coli*. Механизм бактерицидного действия трифенилфосфониевых соединений можно объяснить их способностью вызывать нарушения энергетического обмена у бактерий за счет резкого снижения мембранного потенциала путем стимуляции протонофорного разобщения. На текущий момент случаи устойчивости к SkQ1 среди грамположительных бактерий не зафиксированы, поэтому антимикробные препараты на основе трифенилфосфония могут быть эффективно использованы для борьбы с планктонными и сессильными клиническими штаммами, нечувствительными к обычным антибиотикам.

Antimicrobial resistance threatens the very core of modern medicine. Systematic misuse and overuse of antibiotics in human medicine and food production have put every nation at risk. Without significant effort and immediate global action, the world is heading towards post-antibiotic era in which common and trivial infections could once again kill [1].

The resistance to antimicrobial agents is happening around the world, and leading to a significant decrease of therapeutic options for bacterial diseases. Antimicrobial resistance affects all areas of health, and direct consequences of infection with resistant microorganisms can be severe.

In 2017, the World Health Organization issued a global priority pathogen list [2] to guide efforts to find new antibiotics against the current public health bacterial threats. Gram-positive bacterial pathogens, such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Enterococcus faecium*, are responsible for community-acquired and hospital-associated infections and are an increasing public health threat. Despite causing infections, such bacterial species are also normal inhabitants of human and animal microbiota. To establish infection, these pathogens possess a wide array of virulence factors, which are responsible for successful colonization in human hosts as well as evasion of the immune system. One of the virulence aspects that contributes to the successful infection by these bacteria is their ability to form biofilm, both on biotic (bones and heart valves) and abiotic surfaces (catheters, prostheses and other medical devices) [3–5]. Biofilms can be defined as a sessile microbial community in which cells are attached to a surface and/or other cells and incorporated into the protective extracellular polymer matrix. The process of biofilm formation induces many phenotypic alterations, including loss of motility, reduced growth rate, increased surface adhesion and higher tolerance to antibiotics and host immune response [6]. Thus, biofilm can be associated with chronic and recurrent infections caused by these bacterial species. Due to ability to produce biofilm and high antimicrobial resistance rates found in certain variants of *S. pneumoniae*, *S. aureus* and *E. faecium* strains, therapeutic options are limited. Therefore, the search for new therapeutic approaches is necessary.

Staphylococcus aureus

S. aureus is an important human pathogen and is a leading cause of soft tissue, blood-borne and device related infections in adults and children. Currently, *S. aureus* is the most common bacterial species isolated in intensive care units in the United States [7]. In addition, *S. aureus* is the second most common bacterial pathogen that causes infections in outpatients [8]. At the same time, it can also be found colonizing asymptomatically the skin and nares of approximately 20 % of the population [9]. Risk factors for infection include disruption of mucosal or cutaneous surfaces, introduction of a foreign body or medical device, surgery, hemodialysis or host immunosuppression. Antimicrobial resistance, especially methicillin-resistant *S. aureus* (MRSA), is an important public health problem among *S. aureus* clinical isolates, complicating treatment and prevention of staphylococcal infections. Since its first report in the 1960's, the incidence of nosocomial infections caused by MRSA has been increasing steadily. MRSA can be responsible for nearly 50 % of all reported *S. aureus* hospital-associated infections, being highlighted in surgical site infections and catheter-associated urinary tract infections. Resistance to methicillin, and other beta lactams, in MRSA strains results from the acquisition of the *mecA* gene cassette, which modifies the penicillin binding proteins in the cell wall [10]. More

recently, the emergence of vancomycin-intermediate (VISA) and vancomycin-resistant *S. aureus* strains (VRSA) has further increased the concerns regarding antimicrobial-resistant *S. aureus* infections. The proportion of MRSA strains with reduced susceptibility to vancomycin nearly doubled between 2004 and 2009 [11].

Enterococcus sp.

Enterococci have become important nosocomial pathogens in the last decades, being the third most common opportunistic pathogen in the hospital environment and causing more than 12 % of all healthcare-associated infections [12]. In addition, *Enterococcus* are normal inhabitants of the intestinal microbiota of humans and animals. *Enterococcus faecalis* and *Enterococcus faecium* account for the majority of enterococcal strains recovered from colonization and infections in humans. Enterococcal isolates are frequently associated with resistance to multiple antimicrobials. The occurrence of vancomycin-resistant enterococci (VRE) has peculiar importance due to the high ability for dissemination and association with therapeutic challenges [13]. Resistance to vancomycin is more common among *E. faecium* strains, and is mediated through the acquisition of a group of genes collectively known as the *van* gene complex. These genes are harbored by a transposon and encode an alteration in the cell wall that leads to reduced affinity for vancomycin. VRE isolates can also be highlighted as reservoirs of antimicrobial resistance genes, which can be transferred to other bacterial species, such as *S. aureus*. VRSA strains have acquired the van genotype from enterococcal isolates [14]. Approximately 8 % of colonized patients develop a VRE infection either during or shortly after hospital admission [15], and the associated mortality for these infections can be high (13–46 %) [16]. VRE strains are usually associated with intra-abdominal, skin and soft tissue, urinary tract, bloodstream infections and endocarditis. VRE transmission often occurs via healthcare workers and once acquired may be life-long. Approximately one-third of the reported enterococcal infections were due to vancomycin-resistant strains. Therefore, we cannot rely on the availability of effective antimicrobial agents for treatment of VRE infections and highlight the importance of preventing transmission of these microorganisms.

Streptococcus pneumoniae

S. pneumoniae, also known as pneumococcus, is a significant human pathogen, being the leading cause of community-acquired pneumonia and one of the major agents of bacterial meningitis. This microorganism can be part of the nasopharynx microbiota of healthy individuals, but asymptomatic colonization can evolve to disease once pneumococcus is capable to migrate from the nasopharynx to sterile sites such as the brain, lungs and bloodstream, especially among immunocompromised individuals such as the elderly and young children. Penicillin nonsusceptible pneumococci (PNSP) are currently listed among the most important antimicrobial resistant threats worldwide [2, 17]. Increasing and alarming numbers of PNSP isolates have been detected since the first report in the 1960's. These isolates are usually resistant to different beta-lactam antibiotics, and appear as consequence of the genetic modification of penicillin-binding protein (PBP) genes, leading to the production of PBPs with reduced affinity to beta-lactams. In addition to resistance to beta-lactams, pneumococcal isolates resistant to macrolides have emerged worldwide, representing up to 40 % of pneumococcal isolates

recovered in Europe [18] and more than 70 % of the strains from Asian countries. Resistance to macrolides among pneumococci is mainly attributed to ribosomal target site alteration, but can also be due to alteration in antibiotic transport and modification of the antibiotic [19]. Antimicrobial resistance in *S. pneumoniae* has been modulated by the widespread use of antibiotics and also by the introduction of pneumococcal conjugate vaccines (PCV).

Bacterial energetics is a target for new antimicrobials

The keystone of the bacterial bioenergetics is cellular membrane, which acts as a barrier to allow the energy of electrochemical gradients to transform into pure chemical energy, in accordance with cellular demands. All bacteria require an electrochemical gradient of a proton motive force (PMF) to be consumed by for a variety of processes, such as the synthesis of ATP and active transport of nutrients from the environment for their growth and metabolic activity. Moreover, the generation of the PMF is evolutionarily conserved and existed in the last universal common ancestor (LUCA) [20, 21].

Some chemical compounds, such as gramicidin, can disrupt membranes by forming physical pores, therefore decreasing electrochemical gradients. Other chemical compounds, named protonophores, can decrease electrochemical gradients by specifically binding to protons, characterizing the protonophoric cycling on membranes (Figure, left panel). Still, there is an additional group of chemical compounds able to decrease electrochemical gradients, named protonophore-like compounds (protonophorous uncouplers). Compared to protonophores, protonophorous uncouplers carry another proton-binder across membranes (Figure, right panel), such as fatty acids [22].

Therefore, targeting bacterial bioenergetics by new antimicrobial agents brings new effective possibilities to subvert bacterial infections, especially those caused by antimicrobial resistant variants, by initiating an idle running of bacterial bioenergetics, which is presumably without the threat of the acquisition of resistance.

Triphenyl phosphonium-based substances

Quaternary ammonium and phosphonium compounds have been used as antiseptics and disinfectants for many decades [23–28]. Recently developed mitochondria-targeted antioxidants, a wide range of compounds having an antioxidant group linked to a mitochondria-targeted moiety, are exemplified by triphenyl phosphonium-conjugated chemical groups, such as ubiquinone (MitoQ) [29], plastoquinone (SkQ1) [30]. Such compounds have been reported as effective in killing reference strains of *Bacillus subtilis* [31, 32]. Moreover, SkQ1 demonstrated effectiveness also against certain Gram-negative bacterial species, except *Escherichia coli*, and different Gram-positive species, including *S. aureus*, and *Mycobacterium sp*.

The mechanism of the bactericidal action of triphenyl phosphonium-based antibiotic SkQ1 could be also ascribed to its ability to suppress bacterial bioenergetics by collapsing membrane potential through activation of protonophorous uncoupling. Using *in silico* screening it has been found that antiinfective compounds for treating some parasitic infections are uncouplers for bacteria bioenergetics [33]. Moreover, it was found recently that widely used broad-spectrum biocide triclosan induced collapse of membrane potential in bacterial cells together with well-known inhibition of enoyl-acyl carrier protein reductase, one of the key enzymes in bacterial fatty acid synthesis [34].

SkQ1 contains not only a strong antimicrobial moiety but also an antioxidant moiety targeting mitochondrial reactive oxygen species; therefore, SkQ1 can be considered as a new type of dual-acting "hybrid" antibiotic. The absence of cytotoxicity of 1–2 µM SkQ1 for human and animal cells means that SkQ1 might be safely used to treat many bacterial infections by killing invading bacteria on the one hand, and curing damaged host cells on the other hand.

Such compounds also present potential to be used in bacterial infections where biofilms can be present. To this date, there are no reports of resistance to SkQ1 and alkyl-triphenyl phosphonium among Gram-positive bacteria.

CONCLUSIONS

Relying on the current level of knowledge of mechanisms of bacterial antibiotic resistance and bioenergetic processes in bacterial cells, it is possible to suggest that TPP-based compounds could be potential alternative antimicrobial agents for certain antibiotic-resistant pathogenic bacteria, representing a novel path through which antimicrobial resistance could be subverted and mortality rates associated with such infections could decrease.
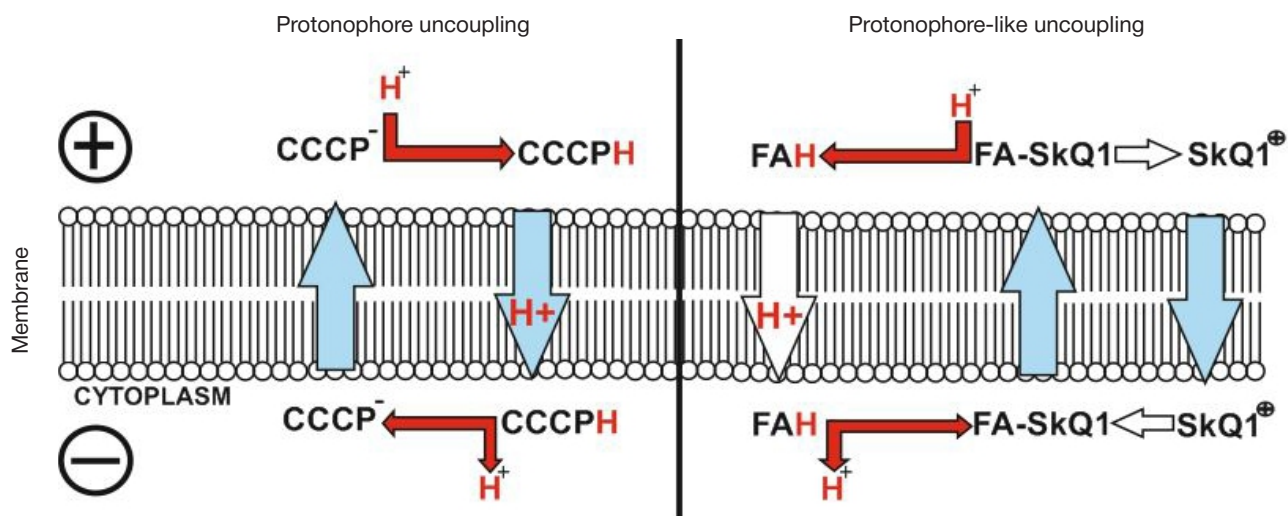
Protonophoric cycling performed by protonophore uncoupler CCCP and protonophore-like triphenyl phosphonium-based coupler SkQ1 with help of fatty acids (FA)

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