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Extended Abstract
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Infectious Diseases Conf 2019 : ATP synthase as a molecular drug target to combat antibiotic resistant microbial infections - Zulfiqar Ahmad, A T Still University, USA

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Antibiotic resistance is posing an existential threat, as it will result in 10 million additional deaths worldwide per year by 2050. Currently, about 700,000 people die every year from microbial infections. Thus, microbial superbugs will become the top global killer, surpassing cancer. The impact of this public health crisis on the global economy is projected to cost $ 100 trillion. The World Health Organization's global report on surveillance of antimicrobial resistance estimated the yearly cost to the US health system to reach $ 34 billion. Fast-encroaching antibiotic resistance by microbes in general and E. coli, in particular, is the main reason for this situation. Thus, finding alternative ways to kill microbes is of paramount importance. Selective inhibition of microbial ATP synthase provides an effective and efficient way to combat antibiotic-resistant microbial infections. Due to their prophylactic effect, they are also used as part of the cocktail of drugs given to treat complex diseases such as cancer or during surgery, in order to prevent infection. This has resulted in a decrease of mortality from infectious diseases and an increase in life expectancy in the last 100 years. However, as a consequence of administering antibiotics broadly to the population and sometimes misusing them, antibiotic-resistant bacteria have appeared. The rise of safe strains is a worldwide wellbeing danger to humankind. Exceptionally safe microscopic organisms like Staphylococcus aureus (methicillin-safe) or Enterococcus faecium (vancomycin-safe) have prompted intricacies in serious consideration units, expanding clinical expenses and putting persistent lives in danger. The presence of these safe strains along with the trouble in finding new antimicrobials has frightened mainstream researchers. The vast majority of the systems right now utilized to grow new anti-microbials point towards novel methodologies for tranquilize configuration dependent on prodrugs or levelheaded plan of new particles. Be that as it may, focusing on pivotal bacterial procedures by these methods will continue making transformative weight towards sedate opposition. In this audit, we examine anti-toxin obstruction and new choices for anti-toxin disclosure, concentrating specifically on new choices planning to incapacitate the microorganisms or engage the host to stay away from malady beginning.

ATP synthase is the fundamental source of cellular energy production for almost all organisms. Inhibition of ATP synthase can deprive cells of required energy leading to cell death. A wide variety of inhibitors including phytochemicals and peptides are known to bind and inhibit ATP synthase. These phytochemicals and peptides bind to the specific binding pockets on ATP synthase. These binding pockets are flanked by many variable amino acids in different organisms. Our lab is identifying and characterizing phytochemicals and peptides as potent and selective inhibitors of ATP synthase to combat the antibiotic-resistant microbial infections using E. coli as a model organism. Method: Wild type, null and mutant E. coli growth properties are being tested on fermentable glucose and non-fermentable succinate carbon sources. Wild type and mutant enzymes were isolated by harvesting cells in minimal media. Inhibitory studies are performed on membrane-bound F1Fo ATP synthase. Several approaches have been developed to fight the problems with current and emerging bacterial resistance. Some of these approaches focus on targeting the same sites as 1st generation antibiotics (bacterial cell wall, the cell membrane or essential bacterial enzymes) with chemically modified antibiotics or with a combination of several antibiotics. Some 2nd, 3rd or 4th generation antibiotics are such modified compounds with improved pharmacological properties but with the same mechanism of action. The main drawback to this approach is that old target sites are usually directly related to essential bacterial processes. This creates a strong adaptation pressure: bacteria will try to readjust to the new environment for its survival. Those individuals with the greater capacity to produce genetic variability will have the greatest potential of

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finding a way to overcome the effect of the antibiotic, leading to the appearance of resistance. In cases where the resistance appears due to mutations in the target site or through the development of efflux pumps which remove the antibiotic out of the bacteria, the problem becomes extremely challenging, as the new analogs are also likely to be affected. Another approach is to find novel mechanisms or novel target sites in bacteria. The search for novel unexploited targets has been the main strategy of the scientific community for years. When selecting a new target, different criteria have to be met: it has to be present in a specific spectrum of bacteria, it has to be druggable and it must not be present in humans in any homolog form. Once the therapeutic target is identified and validated by demonstrating that affecting the target will have a direct bactericidal or bacteriostatic effect, the next step is to find a molecule that is effective against that target and safe enough for use. For example, an enzyme inhibitor or a molecule that interferes with binding to the target. Structural modifications of inhibitors are made through replacement or re-positioning of the functional groups (–OH, –COOH, –NH2, –NO2, –PO4) on phytochemicals or addition of positive charges on the peptides. Wild type and mutant cell growth assays are tested in the presence and absence of inhibitors along with null control. Results: We found that phytochemicals and peptides cause the variable degree of inhibition of ATP synthase. Modification of inhibitors augments the extent of inhibition. In phytochemicals, re-positioning and addition of new functional groups and for peptides, an addition of a c-terminal NH2 group enhances the inhibitory potency. We also observed that the incremental addition of positively charged residues in peptides augments the inhibitory effects of peptides by about 100-fold. The growth of E. coli strains in presence and absence inhibitors suggest that ATP synthase is a potential molecular drug target to combat microbial infections. It is also explored the synergistic inhibitory effects of phytochemicals and peptides on microbial ATP synthase. Conclusion: It is concluded that ATP synthase is a potential molecular drug target and selective inhibition of microbial ATP synthase by phytochemicals and peptides can be used to combat drug-resistant microbial infections.

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