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ATP synthase as a molecular drug target to combat antibiotic resistant microbial infections

Introduction & Aim: 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. 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 the minimal media. Inhibitory studies are performed on membrane bound F1Fo ATP synthase. Structural modifications of inhibitors are made through replacement or re-positioning of the functional groups (–OH, –COOH, $–NH_2$, $–NO_2$, $–PO_4$) on phytochemicals or addition of positive charges on the peptides. Wild type and mutant cell growth assays are tested in presence and absence of inhibitors along with null control.

Results: We found that phytochemicals and peptides cause variable degree of inhibition of ATP synthase. Modification of inhibitors augments extent of inhibition. In phytochemicals, re-positioning and addition of new functional groups and for peptides, addition of a c-terminal NH_2 group enhances the inhibitory potency. We also observed that incremental addition of positively charged residues in peptides augments the inhibitory effects of peptides by about 100-fold. Growth of *E. coli* strains in presence and absence inhibitors suggest that ATP synthase is a potent 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 potent molecular drug target and selective inhibition of microbial ATP synthase by phytochemicals and peptides can be used to combat drug resistant microbial infections.

Biography

Zulfiqar Ahmad has obtained his Doctorate in Biosciences from Jamia Millia Islamia, New Delhi and became Faculty at Hamdard University, New Delhi. In 1998, he has joined as a Postdoctoral Fellow at the University of Rochester Medical Center, NY. In 2006, he was appointed Faculty Position at East Tennessee State University. In 2010, he moved to Alabama A&M University and in 2013 joined A. T. Still University. His research focus is on the role of ATP synthase in human health and diseases, using *Escherichia coli* as a model system. The overall goal of his research is to demonstrate ATP synthase as a viable molecular target against drug resistant bacterial infections.

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