# Polyphosphate synthesis as a target for novel antibiotics

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Inorganic polyphosphate (polyP) is a biopolymer of tens or hundreds of phosphate (Pi) residues linked by highenergy phosphoanhydride bonds. PolyP has been studied mainly in prokaryotes but it is present in all species of the three domains of life. In bacteria, polyP and its processing enzymes play important roles in cellular metabolism as well as in pathogenesis. The genomes of many bacterial species, including pathogens, encode orthologs of the main polyPsynthesizing enzyme, PPK1. This enzyme has been studied in E. coli and its metabolic inhibitors have been reported. The high degree of identity between the PPK1 orthologs in some of the major pathogenic species has prompted the knockout of their ppk1 genes to determine the dependence of virulence on polyP. Although viable, mutants lacking the ppk1 gene have reduced levels of polyP and exhibit multiple structural, functional and virulence defects. The emergence of multi-drug resistant (MDR) bacteria is the result of antibiotic overuse. Therefore, novel approaches are much needed to tackle them. One of these combines the reduction of bacterial virulence while simultaneously increasing susceptibility to host defenses instead of killing the pathogen. Considering that no PPK1 orthologs have been identified in higher-order eukaryotes, PPK1 exhibits an enormous potential as a novel target for antimicrobial drug design. In this review we focus on the current state of the art regarding polyP deficiency in pathogenic bacteria and attempts to design inhibitors targeting enzymes responsible for the synthesis of polyP in bacteria. 

Antibiotics

Chemical biology

In silico drug design

Pathogenic bacteria

Polyphosphate

Polyphosphate kinase 1

Ppk1 inhibitors

Virulence

adenosine 5 phosphate derivative

adenosine diphosphate

adenosine triphosphate

antibiotic agent

bacterial enzyme

guanidine

polyphosphate

polyphosphate kinase 1

polyphosphate kinase 1 inhibitor

polyphosphate kinase 2

pyrophosphate

unclassified drug

antibiotic sensitivity

bacterial gene

bacterial virulence

drug design

drug protein binding

drug synthesis

drug targeting

enzyme inhibition

Escherichia coli

gene deletion

Helicobacter pylori

IC 50

Mycobacterium tuberculosis

Neisseria meningitidis

nonhuman

protein structure

review

Shigella flexneri

Vibrio cholerae

Bacteria (microorganisms)

Eukaryota

Prokaryota