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Investigating the Flavin-Dependent Thymidylate Synthase (FDTS) Enzyme from Clostridioides Difficile (C. diff)

Authors : Sidra Shaw, Sarenna Shaw, Chae Joon Lee, Irimpan Mathews, Eric Koehn

Abstract : One of the biggest public health concerns of our time is increasing antimicrobial resistance. As of 2019, the CDC has documented more than 2.8 million serious antibiotic resistant infections in the United States. Currently, antibiotic resistant infections are directly implicated in over 750,000 deaths per year globally. On our current trajectory, British economist Jim O'Neill predicts that by 2050, an additional 10 million people (about half the population of New York) will die annually due to drug resistant infections. As a result, new biochemical pathways must be targeted to generate next generation antibiotic drugs that will be effective against drug resistant bacteria. One enticing target is the biosynthesis of DNA within bacteria, as few drugs interrupt this essential life process. Thymidylate synthase enzymes are essential for life as they catalyze the synthesis of a DNA building block, 2′-deoxythymidine-5′-monophosphate (dTMP). In humans, the thymidylate synthase enzyme (TSase) has been shown to be distinct from the flavin-dependent thymidylate synthase (FDTS) produced by many pathogenic bacteria. TSase and FDTS have distinct structures and mechanisms of catalysis, which should allow selective inhibition of FDTS over human TSase. Currently, C. diff is one of the most antibiotic resistant bacteria, and no drugs that target thymine biosynthesis exist for C. diff. Here we present the initial biochemical characterization of FDTS from C. diff. Specifically, we examine enzyme kinetics and binding features of this enzyme to determine the nature of interaction with ligands/inhibitors and understand the molecular mechanism of catalysis. This research will provide more insight into the targetability of the C. diff FDTS enzyme for novel antibiotic drugs.

Keywords : flavin-dependent thymidylate synthase, FDTS, clostridioides difficile, C. diff, antibiotic resistance, DNA synthesis, enzyme kinetics, binding features
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