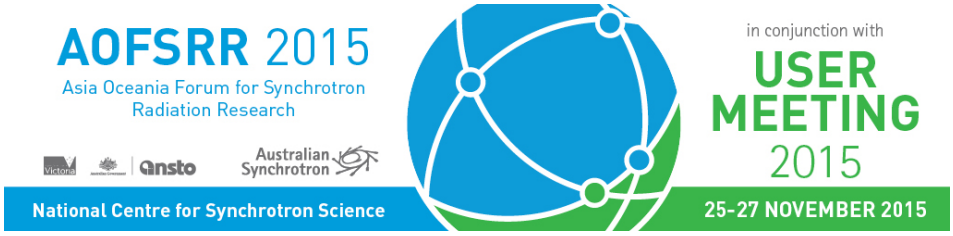

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Structural studies of the Moraxella catarrhalis DOXP reductoisomerase

Friday, 27 November 2015 13:30 (45)

Emerging resistance to current therapeutics and the inadequacies of current treatments for human diseases have led to a strong demand for the development of novel therapeutics. Moraxella catarrhalis is a human mucosal pathogen frequently associated with opportunistic respiratory and middle ear infections. As with other gram-negative bacteria, it relies on the methylerythritol (MEP) pathway for biosynthesis of terpenes, essential secondary metabolites. The MEP pathway is absent in humans providing an attractive target for novel therapeutic design.

The first committed step in the MEP pathway is performed by the 1-deoxy-D-xylulose 5-phosphate (DOXP) reductoisomerase enzyme. We have expressed, purified, performed preliminary kinetic analysis and solved crystal structures of the DOXP reductoisomerase determined in three different forms related to its catalytic cycle. These include a catalytically relevant inhibitory complex with fosmidomycin (a DOXP analogue), which help to delineate features of the active site that could be selectively targeted in the development of inhibitor-based therapeutics. This study provides a strong foundation for the rational design of novel DOXP reductoisomerase inhibitors in the future and provides a new target to alleviate the burden on established anti-bacterial treatments.

Keywords

Structural biology, MEP pathway, Moraxella catarrhalis, anti-bacterial target

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