Poster Presentation

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Mycobacterial Trehalose Synthase as a potential drug target for tuberculosis

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Trehalose synthase (TreS) catalyzes the reversible conversion of maltose to trehalose in mycobacteria as one of three biosynthetic pathways to this non-reducing disaccharide. Given the importance of trehalose to survival of mycobacteria there has been considerable interest in understanding the enzymes involved in its production; indeed the structures of the key enzymes in the other two pathways have already been determined. Herein we present the first structure of TreS from Mycobacterium smegmatis, thereby providing insights into the catalytic machinery involved in this intriguing intramolecular reaction. This structure, which is of interest both mechanistically and as a potential pharmaceutical target, reveals a narrow and enclosed active site cleft within which the intramolecular rearrangement can occur with minimal hydrolysis. We also present the structure of a complex of TreS with acarbose, revealing a hitherto unsuspected oligosaccharide binding site within the C-terminal domain. This may well provide an anchor point for the association of TreS with glycogen, thereby enhancing its role in glycogen biosynthesis and degradation.

[1] *Y. Pan, J. Carroll, N. Asano et al., FEBS J., 2008, 275, 3408-3420,* ***[2]*** *R. Kalscheuer, K. Syson, U. Veeraraghavan et al., Nat Chem Biol., 2010, 6, 376-384,* ***[3]*** *F. Miah, H. Koliwer-Brandl, M. Rejzek et al., Chem Biol., 2013, 20, 487-493*

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