MS06 Structural Enzymology

MS6-02
Time-resolved studies on oxygenase catalysis
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Abstract
The 2-oxogluterate oxygenase structural family are ubiquitous in aerobic biology. They catalyse a very wide range of oxidative reactions, most commonly hydroxylation, but also more exotic reactions, such as penicillin formation from a tripeptide, as catalysed by isopenicillin N synthase (IPNS). They have roles ranging from penicillin biosynthesis in microbes to epigenetic regulations in humans, where they play key roles in hypoxic sensing. Static cryo-crystallography has revealed they have a conserved distorted double stranded beta-helix core fold that supports ferrous iron and 2-oxoglutarate binding residues. Although a consensus mechanism for them has emerged, how the protein fold moves to enable robust catalysis and control the reactivity of intermediates is unclear, though modelling studies suggest correlated motions are important in catalysis. The lecture will describe how XFEL analysis coupled with cryo-crystallographic and solution studies have provided new insight into catalysis by IPNS, including on the role of conformational changes in the protein fold during covalent bond making steps in catalysis. Challenges in initiating and coordinating reaction in crystals will also be discussed.

References
Rabe et al. Sci Adv, 2021, 7, eabh0250