MS02 Infection and Disease/hot structures

MS2-01

B12-dependent radical SAM enzymes: Structural and mechanistic perspectives of emerging catalytic machineries involved in antibiotic biosynthesis and the microbiome

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Abstract

In the last ten years, radical SAM enzymes have emerged as central catalysts for the biosynthesis of myriad natural products including major antibiotics such as carbapenems and antimicrobial peptides (RiPPs). These enzymes are arguably the most diverse and versatile biocatalysts in living systems and represent novel opportunities to face the current antibiotic resistance crisis. Among them, one of the largest and least explored group are the "B_{12}-dependent radical SAM enzymes" with more than 200,000 members identified in genomes and metagenomes. These enzymes use the dual catalytic power of S-adenosyl-L-methionine (SAM) and vitamin B_{12} (cobalamin) to notably form carbon-carbon bonds on unactivated atoms. However, despite years of efforts, we have still a poor knowledge of these enzymes which are the only biocatalysts capable to perform such reaction.

To gain mechanistic insights into these emerging enzymes, we investigated the methanogenesis marker protein 10 (Mmp10) which catalyzes a key post-translational modification (arginine methylation) in methyl-coenzyme M reductase (MCR). By combining biochemical and biophysical techniques including X-ray crystallography and electron paramagnetic resonance, we discovered an unprecedented enzyme architecture containing four distinct metallic centres and key structural features involved in the control of catalysis [1]. Crystallographic snapshots of the reaction showed that, contrary to current paradigm, major and unprecedented active-site reorganization occurred upon following substrate binding in radical SAM enzymes. Notably, we demonstrated that the unique [4Fe4S] cluster can be transiently coordinated by a tyrosine residue which enables the enzyme to alternate between radical and nucleophilic chemistry. This study not only discloses how B_{12}-dependent radical SAM enzymes catalyze chemically challenging alkylation reactions, but also opens new avenues for the biosynthesis and engineering of natural products [2].

References

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