Crystallographic snapshots of Mmp10, a B12-dependent radical SAM methyltransferase involved in methane biosynthesis

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Radical SAM enzymes are the most diverse biocatalysts in living systems. Among them, B12-dependent radical SAM enzymes constitute one of the largest group with more than 200,000 members. These metalloenzymes have the unique property to catalyze the formation of carbon-carbon bonds between unactivated *sp3*-hybridized carbons. To gain insights into the unique mechanism of these emerging biocatalysts, we investigated methanogenesis marker protein 10 (Mmp10), a radical SAM enzyme involved in the post-translational modification of methyl-coenzyme M reductase, the central enzyme for microbial methane formation. By combining spectroscopic investigation (EPR) and structural biology, we showed that Mmp10 is a unique B12 (cobalamin)-dependent radical SAM enzyme. Notably, its structure revealed an unprecedented enzyme architecture with four distinct metallic centers and key structural features involved in the control of catalysis. For instance, major reorganization of its unique [4Fe4S] cluster occurs during catalysis. In addition, the enzyme–substrate complex offers a first glimpse into a B12-dependent radical SAM enzyme in a pre-catalytic state. These crystallographic snapshots allowed to reconstitute the complex mechanism of this unique enzyme and to illuminates how B12-dependent radical SAM enzymes catalyze chemically challenging alkylation reactions. Finally, our study provided a structural rationale for the dual use of the S-adenosyl L methionine (SAM) cofactor for radical and nucleophilic chemistry [1].

1. Fyfe CD, Bernardo-García N, Fradale L, Grimaldi S, Guillot A, Brewee C, Chavas LMG, Legrand P, Benjdia A*, **Berteau O.*** - **2022 -** Crystallographic snapshots of a B12-dependent radical SAM methyltransferase. ***Nature*** (7896):336-342.