

SAM: A helping hand in many places

S-adenosyl methionine (SAM) is increasingly recognised to have widespread roles in biology. One is as a methylating agent, *eg* for histones, but many others involve the reductive formation of the 5'-deoxyadenosyl radical from SAM. Direct demonstration of this radical has proved difficult – see Brindley et al [1] for an attempt. Enzymes utilising this radical are known as radical SAM enzymes and are involved in a range of reactions that require generation of a radical on a target substrate. These enzymes have a characteristic motif for binding an iron–sulfur (FeS) centre. Examples include steps in some heme synthesis pathways, like the reaction catalysed by HemN [2] in an anaerobic route to heme, and the recently described conversion of 12,18 didecarboxysiroheme to Fe-coproporphyrin III, catalysed by AhbC in what is termed the alternate heme biosynthesis pathway [3]. Here, decarboxylation is linked to the generation of a vinyl bond. In another example a radical SAM enzyme is involved in a different type of transformation en route to the *d*₁ heme of a periplasmic nitrite reductase in bacteria [1,3].

One of the newest additions to this class of enzyme is a protein that catalyses the oxidative decarboxylation of the C-terminal tyrosine residue in a ribosomally-synthesised, post-translationally modified peptide found in some microorganisms, including *Mycobacterium smegmatis* and related species. The peptide is encoded by the *mftA* gene, which is clustered with two other genes — *mftB* and *mftC* — in over 300 genomes. The MftC protein, which is known to be critical for growth of *Mycobacterium tuberculosis* on cholesterol, and is a member of the mycofactocin biosynthetic cluster, was predicted based on sequence analysis to be a member of the radical SAM family. Very recently, two sets of investigators, Latham, Khaliullin and colleagues at the University of Denver [4] along with Bandarian and Bruender at the University of Utah [5], with papers in FEBS Letters and Biochemistry respectively, have shown that MftC, provided it is in the reduced state, and that the MftB protein is also present, can catalyse the oxidative decarboxylation of the C-terminal tyrosine of MftA (Fig 1). The work in each case relied on modern methods of mass spectrometry to identify the modified MftA product that is formed by loss of a carboxyl group and generation of an ethenic bond. Both research groups envisage a similar mechanism (Fig 1) [4,5], but Bruender and Bandarian [5] also contemplate a variant in which the unpaired electron shown in the '•COOH' species is lost to the FeS center of the enzyme, such that CO₂ is released. The reduced state of the FeS center is necessary for the generation of the 5'-deoxyadenosyl radical. Pathways for reduction of the FeS centers of radical SAM enzymes is an aspect that remains to be fully clarified.

It is remarkable that two research groups have identified a new function of a radical SAM protein simultaneously; but this illustrates the growing recognition of the importance of this class of enzyme.

1.Brindley AA, Zajicek R, Warren MJ, Ferguson SJ & Rigby SEJ (2010) NirJ, a radical SAM family member of the d₁ heme biogenesis cluster.FEBS Letters 584, 2461-2466

2. Layer G, Verfurth K, Mahlitz E, Jahn D (2002) Oxygen-independent coproporphyrinogen-III oxidase HemN from *Escherichia coli* J. Biol Chem 277, 34136-34142
3. Bali S, Lawrence AD, Lobo SA, Saraiva LM, Golding BT, Palmer DJ, Howard MJ ; Ferguson SJ ; Warren MJ (2012) Molecular hijacking of siroheme for the synthesis of heme and *d*₁. Proc Natl Acad Sci US 108, 18260-18265
4. Khaliullin B, Aggarwal P, Bubas M, Eaton GR, Eaton SS, Latham JA (2016) Mycofactocin biosynthesis: Modification of the peptide MftA by the radical S-adenosylmethionine protein MftC. FEBS Letters,
5. Bruender NA & Bandarian V (2016) The radical S-adenosyl-L-methionine enzyme MftC catalyzes an oxidative decarboxylation of the C-terminus of the MftA peptide. Biochemistry 55, 2813-2816

Fig. 1. Transformation of the C-terminus of MftA by the action of MftC. As shown SAM plus reductant, presumably the FeS centre in MftC initiates radical chemistry. As discussed in the text, an alternative mechanism envisages return of the unpaired electron to the FeS centre.

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