Introduction to the Thematic Mini review Series on Radical S-Adenosylmethionine (SAM) Enzymes*

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In the early days, radical enzyme reactions that use S-adenosylmethionine (SAM) coordinated to an Fe-S cluster, which Perry Frey described as a “poor man’s coenzyme B12,” were believed to be relatively rare chemical curiosities. Today, bioinformatics analyses have revealed the wide prevalence and sheer numbers of radical SAM enzymes, conferring superfamily status. In this thematic mini review series, the JBC presents six articles on radical SAM enzymes that accomplish wide-ranging chemical transformations. We learn that despite the diversity of the reactions catalyzed, family members share some common structural and mechanistic themes. Still in its infancy, continued explorations promise to be fertile grounds for discoveries that will undoubtedly further broaden our understanding of the catalytic repertoire and deepen our understanding of the chemical strategies used by radical SAM enzymes.

Most members of the radical SAM superfamily harbor a conserved C3X2C3X2C [4Fe4S] cluster motif, which binds SAM via direct coordination. This structural arrangement facilitates reductive cleavage of the C=chlorine SAM to give the 5′-deoxyadenosynol radical, which initiates the radical-based chemical transformation catalyzed by the specific enzymes. In the first article in the series, Drennan and co-workers (1) review the SPASM and Twitch domain-containing family members. These folds extend from the common structural core and bind auxiliary Fe-S clusters enabling functional diversification. Structures of SPASM and Twitch domain proteins are used to make mechanistic predictions about other family members for which structures are currently unavailable.

The chemical challenge of inserting sulfur at unactivated carbon is met by deployment of radical SAM enzymes. In the second article in this series, Joseph Jarrett (2) discusses gains in our understanding of sulfur insertion chemistry during biosynthesis of the cofactors, lipoic acid and biotin, methylthiol insertion into tRNA and proteins, and thioether bond formation in sactibiotics, sulfur-bridged bacteriocins. Biotin synthase and lipoate hydrolase appear to sacrifice auxiliary Fe-S clusters as a source of sulfur. In contrast, the sulfur source for the methylthiol modification is unclear and could be sulfide, persulfide, or a polysulfide species, whereas the methyl group is derived from SAM. Radical generation at the α-carbon where the thioether bond is to be formed and subsequent quenching by the cysteine sulfur in the peptide substrate leads to the cross-linked sactibiotic product.

In the third article in this series, Begley and co-workers (3) discuss the role of radical SAM enzymes in facilitation of complex radical rearrangements during the synthesis of thiamin, deazaflavin, menaquinone, molybdopterin, and heme cofactors. In this article, the authors discuss how the relatively long lifetime of the 5′-deoxyadenosynol radical, together with its intrinsic reactivity, opens up a range of novel reactions including fragmentation, double bond addition, and radical propagation, some of which are unprecedented in organic chemistry.

The elaboration of unusual organometallic cofactors requires unusual enzymes. In the fourth article in this series, Broderick and co-workers (4) discuss the current state of our knowledge about radical SAM enzymes involved in the synthesis of the FeMo cofactor of nitrogenase, which contains a central carbon atom, the iron subcluster coordinated by cyanide, CO, and dithiomethylnine in [FeFe]-hydrogenase and the iron center with CO and guanyllylpseudonol ligands in [Fe]-hydrogenase.

In the fifth article in this series, Booker and co-workers (5) review the complexity of radical SAM enzyme-catalyzed methylation reactions. The methylases are classified depending on whether they use two cysteine residues (Class A) or two SAM molecules (Class C) to methylate sp3-hybridized carbons or require a cobalamin cofactor (Class B) to methylate either sp2-hybridized or sp3-hybridized carbons or phosphinate phosphorus atoms. The review also covers the recently described Class D methylases, which are postulated to methylate sp2-hybridized carbon centers using methylenetetrahydrofolic acid.

UV light takes its toll on DNA, cross-linking strands and arresting replication. Dimerization of proximal pyrimidines is the common mechanism for UV-induced structural distortion. In bacterial endospores, UV induces a novel thymidine dimer, which is repaired by spore photoprotein lyase, which utilizes a radical SAM-dependent mechanism to resolve the dimer into individual thymidine residues. In the final review in this series, Yang and Li (6) discuss that although the reaction mechanism can be drawn by broad strokes, the intricacies of the repair reaction remain to be elucidated.

REFERENCES
