

including mammalian cells.^{19,20,84–87} SAM superfamilies have many different structural domains and folds without obvious homology that perform all these varied chemical reactions. These families probably date back to a common ancestor of bacteria, archaea, and eukaryotes.^{19,20} It has been estimated that ~95% of SAM is used for methylation and 3–5% for the generation of decarboxylated SAM (dcSAM) for polyamine synthesis,⁸⁸ leaving only ~1–2% for use by many other crucial enzymes with perhaps only a few copies per cell, but with major impact.^{20,89} In humans, 85% of all of methylation reactions and 50% of all methionine metabolism takes place in the liver.⁹⁰

18.2.2 Structures of SAM-Dependent Enzymes

The majority of SAM-dependent methyltransferases (MTases) share a common structure, the Rossmann fold, which is conserved in evolution, though the residues that contact SAM are not (see ref. 14,19,84–86 for reviews). Classification of this large superfamily is based on substrate specificity, and on the atom targeted for methylation (*e.g.* N, O, C, or S). Several proteins contain the Rossmann fold despite being inactive as MTase, *e.g.* spermidine synthase.⁸⁴ A triose phosphate isomerase-like domain (called the TIM barrel) is present in radical SAM enzymes, which use SAM to generate methionine and a 5'-deoxyadenosyl radical that can be used to generate further radicals on the same or another protein (see Section 18.5.2).^{19,20} A third class of SAM-dependent enzymes contains the SET domain. This domain was discovered as a conserved domain shared by the chromatin remodeling protein suppressor of variegation 3-9 (Su(var)3-9), enhancer of zest and trithorax. These enzymes affect chromatin function and transcription by methylating lysines in *e.g.* histones and P53.¹⁹ The SPOUT fold was originally identified as a domain shared by the SpoU and TrmD MTases in a superfamily of enzymes that methylate tRNA and rRNA.^{91,92} Archaeal Tsr3 has a distinct SAM binding mode and modifies a conserved hypermodified nucleotide in eukaryotic 18S rRNA.⁹³ Some enzymes in the methionine cycle have unusual folds: *e.g.* MAT proteins (involved in *de novo* synthesis of SAM), methionine synthetase (MS, which regenerates methionine using the methyl group from methyltetrahydrofolate (MTHF)), and the repressor of the methionine operon, MetJ.¹⁹

18.3 Well-Known Pathways of SAM in Central Metabolism

18.3.1 The Methionine Cycle

As mentioned in Section 18.2.1, ~95% of SAM is used for methylation. In the methionine cycle (also called one-carbon or SAM cycle) demethylation of SAM yields *S*-adenosylhomocysteine (SAH). SAM is regenerated *via* a homocysteine (HCY) intermediate, in turn the substrate for MS with vitamin B12 as the cofactor and MTHF as the methyl donor, and the cycle is completed by MAT (Figure 18.2). The name 'folate,' the precursor for MTHF, describes a family of related molecules capable of one-carbon transfer. Folate-derived