

all prokaryotes synthesize PQQ, but *e.g.* *E. coli* can use it in an alternative sugar transport system.²⁴³ PQQ is available as a probiotic and food supplement.²⁴⁴ In contrast to most radical SAM enzymes, PqqE of AM1 is markedly oxygen-tolerant.²⁴⁵ Recently, a PQQ-dependent enzyme was identified in mushrooms, with possible homologues in bacteria, archaea, fungi and other organisms.²⁴⁶ From its humble activity in sugar transport in *E. coli* thirty years ago,²⁴³ current reports link PQQ to oxidative stress and diseases that affect life span and aging, *e.g.* inflammation, liver disease, neurological disease, osteoarthritis, diabetes, and mitochondrial functioning, claims that warrant further investigation.^{247–262}

Synthesis of enzymes that cleave C–C, C–N, and C–S bonds include proteins involved in central metabolism and antibiotic synthesis, but also SPL (spore photoproduct lyase), which can repair UV-induced thymine dimers in the absence of light.²⁰ Biosynthesis of chlorophyll photosynthetic pigments requires additional FeS proteins, including methylation by radical RSMT of the tetrapyrrole ring.²⁰ Another example of a complex formation is the molybdene-containing ‘FeMo-co’ [MoFe₇S₉C] cluster in nitrogenase that catalyzes the reduction of nitrogen in our atmosphere to NH₃.²⁰ On a different track, human viperin (RSAD2/Cig5) belongs to the group of interferon-stimulated genes, which act as defense against (dsRNA and DNA) viral and bacterial infections, but may also be involved in pregnancy and atherosclerosis.²⁰ Diphthamide is a modified histidine in elongator protein Elp2 in archaea and eukaryotes, and the target of diphtheria toxin.²⁰ The *dph* gene products are linked to various cancers, and Dph1 knocked out mice are inviable.²⁶³

18.5.4 Radical SAM Methyltransferases (RSMT)

Some SAM-dependent MTases do not have the Rossmann fold (Section 18.2.2), but are radical SAM MTases (RSMT). Three classes, A, B, and C, have been identified.²⁰ Class A Cfr (chloramphenicol-florfenicol resistance) of *Staphylococcus aureus* has a single radical SAM domain. It uses a conserved cysteine to transfer a methyl group of one SAM molecule to 23S rRNA using a radical generated *via* a second SAM molecule. The likely homologue in *E. coli*, RlmN, also methylates 23S rRNA, but does not confer antibiotic resistance.²⁰ Class B RSMT contain both a radical SAM domain and a cobalamin-binding domain.^{20,264} One SAM molecule is probably used to methylate the cobalamin cofactor using a radical generated with a second SAM molecule. The first enzyme identified of this class was TsrM from *Streptomyces laurentii*, a tryptophan MTase involved in the synthesis of thiostrepton A, which targets various pathogenic bacteria, malaria, and possibly even cancer.²⁰ All may not be what it seems: TsrM is a class B RSMT, but does not catalyze SAM-based radical chemistry, while another enzyme in this class may be involved in plasma membrane rigidity, requiring further investigations.²⁰ Class C RSMT contain a radical SAM domain and a C-terminal domain resembling the HemN domain, involved in heme synthesis. The bleomycin biosynthetic genes belong to this class, which make thiopeptides and antibiotics, and may