also use Trp as a precursor (like TsrM). Both these and Yatakemycin (YtkT), a naturally occurring antitumor agent, are of clinical interest against drug-resistant bacterial pathogens, some fungi and cancer.[20]

18.5.5 Radical SAM Methylthiotransferases (MMTases)

Translational fidelity depends on RNA-post-translational modifications, including conserved methylthio modifications on ribosomal protein S12 (*e.g.* RimO on an aspartic acid residue), and on the anticodon in tRNAs reading codons beginning with U (*e.g.* MiaB on $tRNA^{phe}$).[20] MiaB and RimO use two molecules of SAM (one for the generation of a 5′ adenosyl radical, the other as methyl donor, as above).[20] Sequence analysis reveals five families of MMTases in different kingdoms: MiaB (bacteria and eukaryotic organelles), RimO (bacteria), MtaB (eubacteria), e-MtaB (archaea and eukaryotes) and MTL1 (epsilon-proteobacteria). Studies with a human e-MtaB (CDKAL1) and the corresponding knockout mouse indicate a role for CDKAL1 in the prevention of frame shifts and/or misreading. Improper translation might prevent proper processing and folding of *e.g.* proinsulin to insulin, which will influence the onset of type 2 diabetes (see ref. 20 for details).

18.5.6 The Special Case of Elp3

Elp3 was identified as the histone acetyltransferase (HAT) component of the elongator complex that associates with RNA polymerase II during transcriptional elongation.[265–272] The six-subunit elongator complex is conserved in eukaryotes including plants, while archaeal Elp3 catalyzes the wobble uridine in tRNA on its own in the absence of other Elp proteins.[273] In *Toxoplasma gondii* a single Elp3 protein is found with a C-terminal transmembrane domain, which localizes Elp3 to the mitochondrion, and is essential for parasite viability.[268] In plants, elongator is required for the modification of stress response tRNAs for efficient translation and protection against infection ('plant immunity'), *e.g.* threats caused by the fungus *Fusarium graminearum*, which causes serious loss of cereal crops and is toxic to humans and animals, and the brown planthopper, a major rice pest.[274–278] In addition to the C-terminal HAT domain, Elp3 has an N-terminal radical SAM domain, which is important for the activity and structural integrity of the elongator complex.[279–281] Elp3 acetylates histones in the nucleus but also modifies tRNA.[282–285] The resemblance of Elp3 to other proteins with a similar two-domain structure suggested an additional role for Elp3 as a radical SAM histone demethylase,[279,286] which was supported *in vivo*.[286,287] Considering its manifold roles, it is not surprising that Elp3 mutations are linked to disease. Elp3 has attracted much attention by its link to actin-rich domains and mitochondrial dysfunction in neurodegenerative disease *e.g.* familial dysautonomia, and motor neuron disease (amyotrophic lateral sclerosis, ALS).[283,288–293] Elp3 has also been implicated in colon and breast cancer.[294,295] In *Drosophila melanogaster* Elp3 is essential for viability, normal development