18.4 SAM and RNA-Based Control by Riboswitches

18.4.1 Discovery of SAM Riboswitches

Several decades ago Tina Henkin reported a common mechanism with respect to the regulation of some aminoacyl-tRNA synthetase and amino acid biosynthesis genes in gram-positive bacteria, which involved transcription antitermination at a conserved region in 5′ mRNA leader regions.[154,155] This led to the identification of conserved motifs in genes for synthesis of methionine and cysteine.[156] These motifs were recognized by a small SAM-dependent, highly structured, RNA called riboswitch or aptamer, which prevented binding of the 30S ribosomal subunit to the mRNA in the presence of SAM.[157–159] Currently seven different SAM riboswitches, called S-boxes or SMK, are known and are involved in methionine synthesis, as expected, but also sulfur metabolism and other pathways.[158,160–178] Riboswitches may be sensitive to SAM or its metabolite SAH,[177,179] or work in tandem, *e.g.* SAM-I and a B12 riboswitch.[171,173,180,181] Other metabolite-dependent riboswitches for *e.g.* thiamine, purine, glycine, THF, vitamin B12, uncharged tRNA, and SAM are common in bacteria (reviewed in ref. 170,172,182–186) and some have been described in plants, fungi, and marine eukaryotes.[158,170,187] The thiamine pyrophosphate (TPP/vitamin B1) riboswitch occurs in all three domains of life.[188–193] Interestingly, this riboswitch blocks ribosome binding or terminates transcription in bacteria, but appears to regulate gene expression in eukaryotes *via* alternative RNA splicing.[188,194] Will there be SAM-dependent (alternative) splicing to be discovered in humans?

18.4.2 SAM and Other Riboswitches

Several riboswitches affect SAM metabolism indirectly, *e.g.* ZTP riboswitches are members of a large family of regulatory RNAs that upregulate *de novo* purine synthesis in response to increased intracellular levels of ZMP or ZTP (5-aminoimidazole-4-carboxamide riboside 5′-triphosphate). ZMP is an important intermediate in purine biosynthesis and is linked to folate stress *via* the regulation of the levels of a key component of one-carbon metabolism, N10-formyl-THF.[195,196] By 2006, the first structures of riboswitches had become available, as well as riboswitches that *e.g.* control expression of a reporter gene or splicing in yeast,[174,189,197–212] though the latter use of reporters controlled by antibiotics such as tetracyclin needs careful evaluation.[213–215] There is probably no end to the amazing roles of these small RNAs, as they may sense magnesium,[189] or link to repeat expansion, and neurological disease in mammals (see *e.g.* ref. 216 and 217). Batey[172] compared the riboswitch with the IRES, the highly structured mRNA region in important mammalian genes such as ODC, insulin-like growth factor (IGF)-2, and c-myc.[218–220] The question raised by the story of the TPP riboswitches is inevitable: Will RNA structures that bind SAM and thus control gene expression appear on the human horizon and dictate the activity of non-coding and microRNAs?