member of radical SAM enzymes with the 'SPASM' domain,[427,430,431] see ref. 418 for details. These bacterial sulfatases are probably involved in access to carbon sources in the GI tract, cofactor biosynthesis, and post-translational modifications, suggesting a role in disease like that of human sulfatases.[419–421,426,432–434] Taken together, it is "likely that the central role of radical SAM enzymes in the human microbiota is just emerging."[418]

18.7 Conclusions

The involvement of SAM in methylation, transsulfuration and polyamine synthesis already placed SAM at the heart of metabolism and aging a decade ago.[7,17] Epigenetic regulation affects metabolism at the DNA level, but also the flux through the many SAM-dependent pathways, which contributes to (immune) disease, tumorigenesis, and aging.[114,435] The tremendous progress made in recent years now allows us to start to understand how interconnected the SAM routes are with each other and, especially, with ancient biochemistry *via* riboswitches and radical SAM enzymes. With respect to the latter, it will be interesting to see whether some SAM-dependent riboswitches affect eukaryotic splicing like TPP riboswitches (Section 18.4.1), or radical SAM enzymes respond to PARP like DDX11 and FancJ,[336] and/or are capable of sensing DNA damage like XPD (Section 18.5.7). The necessity for growth, maintenance and repair of cellular components requires multilevel control of DNA, RNA, and protein synthesis with a concomitant careful distribution of energy resources. Switching from growth to maintenance to increase health and life span[436–446] appears to be especially linked to a careful balance between the methionine cycle and transsulfuration route, which relies on SAM (see *e.g.* Sections 18.3.2 and 18.6.3). SAM is involved in stress responses (Section 18.5.3) and good stress management, inter- and intra-cellular communication, and mitochondrial functioning will slow down aging and enhance longevity, which may profit from pharmacological intervention.[435,446–452] SAM is implicated in the usefulness of a compound like resveratrol, which affects MAT2B and SIRT1, and mitochondria,[453–455] and may improve insulin sensitivity in obese mice and humans.[456] SIRT1 links mitochondrial respiration with genome stability, immunity, cell death, and energy metabolism (see *e.g.*[457,458] and elsewhere in this volume). SAM is also linked with SIRT1 *via* synthesis of *e.g.* PQQ (Section 18.5.3).[251] Mutants fail to maintain a proper balance between protein synthesis and energy availability.[77,457,459–461]

Many questions remain and certainly new discoveries will be made in the not too distant future. Obesity is a growing problem in modern society with unresolved issues of causality (apart from over-eating). Do humans run a higher risk of becoming obese due to early exposure to antibiotics, as mice appear to do?[462–464] And are artificial sweeteners a risk for glucose intolerance in humans by changing the microbiome, as they appear to do in mice?[465] Medication that supports the observed effects of caloric restriction, changes in lifestyle and food intake, and exercise, will be the best pharmacological intervention strategy to promote, and maintain, the health of the body and