or inflammatory factors, which alter nutrient sensing, energy metabolism and redox status, impair tissues and stem cells, and contribute to aging, neurodegeneration, and cancer.[50–64] There is increasing evidence that levels of food intake and exercise are important factors in health and disease. Diet-induced senescence may be reduced by exercise,[65] and removal of senescent cells could be beneficial, though indiscriminate targeting of senescent cells may be harmful.[66–71] Senescence also occurs in plants as older leaves become senescent in an orderly, SAM-dependent way,[72] which may be nature's way to prepare for programmed renewal.

Anti-aging processes to prevent DNA damage and enhance repair require energy (a human body receives ~10 000 hits in the DNA per day) and nutrient sensors (*e.g.* mammalian target of rapamycin (mTOR)), which is supported by studies on premature aging.[52,55,73–76] SAM is implicated in two mouse models on premature aging (mentioned in ref. 17). Caloric restriction influences longevity and delays age-related diseases, *e.g.* arthritis, cardiovascular disease (CVD), diabetes, obesity, neurodegeneration, muscle atrophy, and osteoporosis.[77–83] It also helps to maintain colon health and lowers the incidence and progression of cancer, which implicates the microbiome, a topic of much current interest (see Sections 18.6.4 and 18.6.5).

18.1.3 This Review

This review starts with the three well-known functions of SAM in the methionine cycle, transsulfuration and polyamine pathways.[7,17] These routes are targets for pharmacological interventions of key enzymes in these pathways *via e.g.* difluoromethylornithine (DFMO) or hydroxylamines (see Section 18.7). The review focuses on recent developments of radical SAM enzymes in central metabolism that affect aging. Exciting new findings suggest novel roles for SAM in RNA metabolism and control of vital functions, more than could have been anticipated a decade ago. These SAM-dependent enzymes are found in ancient processes in all organisms looked at: (eu)bacteria, archaea, yeast, (in)vertebrates, and mammalian cells, while some other functions appear to be newly designed in higher eukaryotes. An important common theme of these routes is the role of sulfur, a pivotal compound before the advent of atmospheric oxygen and more sophisticated macromolecules. These pathways are under very tight control and are carefully monitored by multilayered maintenance and repair routes to prevent disease and aging. Due to lack of space, original papers are sparingly listed and the reader is referred to reviews for further reading.

18.2 SAM-Dependent Enzymes

18.2.1 Parts of SAM Used by SAM-Dependent Enzymes

Different parts of SAM are used in transfer reactions: methyl, methylene, amino, and aminopropyl groups, as well as radicals.[17] Some of these reactions have been identified in bacteria and await unraveling in other organisms,