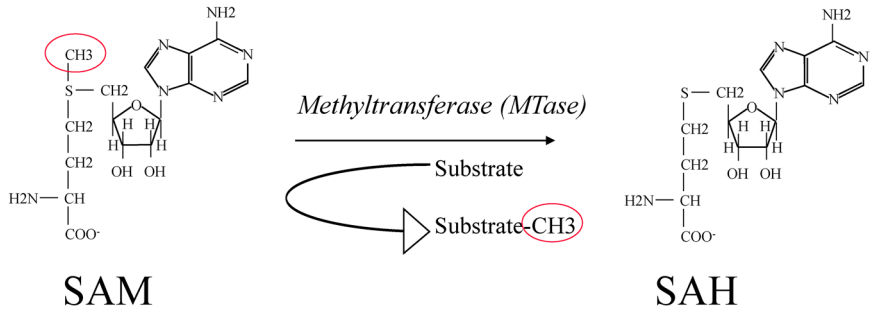

Figure 18.1 *S*-Adenosylmethionine (SAM) is the universal methyl donor. SAM is the major methyl donor used for transfer by methyltransferases (MTases) to DNA, RNA, protein, lipids, small molecules, arsenic, *etc.* SAM is converted to *S*-adenosylhomocysteine (SAH). The methyl group is indicated with a circle.

classified, that of the radical SAM enzymes,[18] which use an FeS cluster for radical chemistry for many purposes.[1,20] As a universal multi-tasker in biochemical transfer reactions, SAM is one of the most frequently used substrates after ATP.

18.1.2 SAM and Aging

What determines aging and life span? Life span may range from days to >100 years, and depends on both genes and environment, and the number of cell divisions.[21–26] In *Escherichia coli* SAM is essential for the assembly of the septal ring during cell division,[27–30] while extracellular communication and longevity are also linked to SAM *via* a process called quorum sensing, which affects virulence and involves *e.g.* AI-2 synthase.[17,31–34] Environmental sensing may also contribute to longevity by triggering pathways involving *e.g.* insulin and Daf-16/FOXO in *Caenorhabditis elegans*.[31] Aging depends on maintenance of genome stability and epigenetic markings, and shows conserved stress-related features. How this is orchestrated is becoming increasingly clear.[35] In eukaryotes, stem cells contribute to the aging process as numbers and the ability to self-renew decline over time in adult tissues.[36–40] Disruption of maintenance methylation causes disease by affecting expression of oncogenes and tumor suppressor genes, and interactions with histones. In addition, endogenous metabolism causes stress by errors during growth and replication, which results in damage to DNA, which indirectly enhances damage to other cellular components, impairs maintenance, and reduces life span.[41–48] Mitochondria play a major role in this redox balance, which shifts to a more oxidized state during aging. Thioredoxin is the major reductant to keep the redox balance, reduce stress and enhance longevity by harnessing the generation of free radicals (ROS) while generating energy.[49] Minor DNA damage provides time for repair, but if repair is too slow or impossible, this results in metabolic malfunction, and either apoptosis ('programmed cell death') or cellular senescence (permanent cell cycle arrest). Senescence often induces prolonged stress signaling *via* cell–cell contact and soluble growth