problems, as well as premature aging and AD, as a result of an imbalance in the flux through the methionine cycle in favor of transsulfuration.[388–391] Overexpression of superoxide dismutase (SOD1) in DS causes chronic stress and protein instability in red blood cells due to damaged asparagine residues, which cannot be properly repaired by a specific SAM-dependent MTase.[388] Hence in this case it is radical damage to proteins that requires a SAM-dependent MTase for repair. Whether altered SOD1 expression in patients with ALS, or that of SOD2 in tumor cells, also lack such SAM-dependent repair remains to be investigated.[392,393]

18.6.3 SAM and Long-Lived Rodents

The Ames dwarf mouse is a long-lived mouse with an enhanced flux towards the transsulfuration pathway in several organs, which is due to a pituitary gland problem and lack of growth hormone (GH).[130] This affects tissue levels of SAM and SAH *via* glycine-*N*-methyltransferase (GNMT).[130] SAM and folate control GNMT: low food intake of SAM inhibited GNMT and made more SAM available for methylation. When SAM was high, GNMT demethylated SAM, thus reducing SAM levels and fueling the transsulfuration route. This and other data supported the notion that longevity of these mice was linked to a better defense against oxidative stress *via* higher GSH levels. Other recent reports also link GH (and insulin) levels to aging in these mice.[394–400]

The naked mole rat is a small native rat in East Africa with an incredibly long lifespan of >30 years. It has the hallmarks of longevity, being very healthy with a stable genome, and little or no signs of senescence or cancer (see *e.g.* ref. 401–406 for some recent references). As H_2S has been implicated in aging and lifespan in diet-induced longevity models, the blood of this rat was compared with that of five mammalian species with different life spans.[131] This revealed an inverse correlation between blood sulfide levels and longevity, which was linked to SAM *via* CBS. As mentioned before, SAM activates CBS and thus stimulates the transsulfuration route (Section 18.3.2). In the naked mole rat, SAM activated CBS to a higher degree compared to the other species, which warrants further investigation.[131]

18.6.4 SAM, the Microbiome and Aging

Microorganisms (microbiota, collectively called the microbiome) are essential in living beings, from humans to worms, flies, and coral, but also in symbiosis with plants.[407–410] They have a beneficial effect on host metabolism and the immune system by providing nutrients and energy (like mitochondria and chloroplasts, which are symbionts that originated from bacteria), and do jobs the host cannot do: *e.g.* fix nitrogen, degrade cellulose, and harvest light. In humans, microbiota break down dietary fiber, produce essential vitamins and amino acids, and detoxify harmful chemicals. Especially B vitamins, including B1, B6, B12, and folate (B9), are important and are intertwined with SAM-dependent cycles and pathways. Often the microbiome