of XPD "may reflect a general biological role for DNA charge transport",[350] which may bring new treatments for patients.[348,351] Are radical SAM enzymes perhaps also capable of such lesion detection?

18.6 SAM and Aging

18.6.1 SAM, Mitochondria and Aging

Harmful effects of ROS radicals like superoxide and hydrogen peroxide are particularly bad news for mitochondria, and hence life span.[352,353] Mitochondria play an important role in aging: (a) Mitochondrial DNA is more vulnerable to damage than nuclear DNA, as repair depends on pol-gamma and is lower than in the nucleus. (b) Mitochondria cannot make SAM, which has to be imported by mitochondrial carriers involved in SAM metabolism, including SAM itself, ornithine, folate, and ATP/ADP exchange.[354] SAM depletion affects the production of GSH and increases mitochondrial instability, though unfortunately methionine supplements may enhance ROS.[354–357] (c) ROS crosslinks Cys residues in mitochondrial proteins, resulting in degradation unless rescued by repair enzymes and GSH.[358] In line with this, long-lived mice tend to have higher mitochondrial GSH levels.[359] Increased GSH production and potential decreased availability of SAM for methylation delays aging and affects development, as *e.g.* shown after overexpression of the rate-limiting enzymes in the transsulfuration pathway in *Drosophila* (GCLC and GCLCM).[352] In two of the three MAT enzymes, oxidation of Cys^{150} reduces MAT activity (mentioned in ref. 352), which taken together make a strong case for a link between SAM and longevity due to altered flux through the transsulfuration route.

Fungal PaMTH, which methylates flavonoids in *Podospora anserina*, accumulates in the mitochondrial matrix of senescent cells and may protect against oxidative stress and aging as overexpression increases life span.[360–363] Such post-translational modifications are not confined to this fungus, as *e.g.* mitochondrial ATP synthase was differentially affected in both *P. anserina* and in the brains of young *versus* old rats, as well as in human cells.[364,365]

18.6.2 SAM and Neurodegeneration

Deregulation of the methionine cycle has been reported in Alzheimer's disease (AD) and other neurodegenerative diseases, such as ALS (see ref. 17,366–382 and OMIM at[383] for further details). Lowered expression of the presenilin 1 (PS1) gene in AD is linked to the accumulation of amyloid-beta, characteristic for this disease.[366] Mildly elevated plasma levels of HCY in elderly people not only increased the risk of AD and neurodegeneration, but also cerebrovascular disease.[384–386] Parkinson's disease is a motor disorder due to loss of dopamine-producing cells in the brain, which leads to neurodegeneration due to methylation of dopamine by catechol-*O*-methyltransferase (COMT).[387] Down's syndrome (DS) people suffer from mental retardation and heart