to faulty (de)methylation, *e.g.* systemic lupus erythematosus (SLE) is linked to overexpression of the ligand of CD27,[105] as a result of decreased promoter methylation.[106–120] SAM supplements sometimes ameliorate disease,[121] but may contain the biologically active *S*,*S* form of SAM as well as the inactive and possibly toxic *R*,*S* molecules.[122] Finally, SAM methylates and detoxifies compounds such as arsenic.[123–125]

18.3.2 The Transsulfuration Pathway to Glutathione

Cystathionine beta-synthase (CBS) can divert HCY from the methionine cycle to generate glutathione (GSH) *via* the transsulfuration pathway with vitamin B6 as the cofactor.[124,126,127] (Figure 18.2). GSH is a ubiquitous tripeptide with antioxidant and detoxification properties. Keeping the balance between methylation and transsulfuration is important to prevent disease, and depends on methionine levels and allosteric activation of CBS by SAM. High methionine levels favor transsulfuration to cysteine and GSH, while low levels favor methylation. In the latter case, decreased binding of SAM to CBS destabilizes the protein, and thus CBS affects viability under conditions of oxidative stress. The conserved SAM-binding domain of CBS probably functions as a metabolic sensor, and mutations in this CBS domain are linked to human disease, which may benefit from manipulation of GSH synthesis.[127–129] The methionine flux to transsulfuration is involved in longevity of certain rodents, *e.g.* the Ames dwarf mouse and the naked mole rat (see Section 18.6.3).[130,131]

18.3.3 The Polyamine Pathway

An estimated 3–5% of SAM in the cell is used by SAM decarboxylase (SAMDC) to generate dcSAM, the substrate for the synthesis of the polyamines spermidine and spermine from putrescine (Figure 18.2). Already observed by Van Leeuwenhoeck in 1678 as crystals in semen, these positively charged molecules bind negatively charged molecules in the cell, including DNA, RNA, proteins, phospholipids, and many other molecules. Ornithine decarboxylase (ODC) and SAMDC are rate-limiting in this carefully regulated pathway, which is important to maintain proper polyamine levels in the cell to remain alive and healthy (see *e.g.* ref. 19,132–146). Regulation involves polyamine-dependent programmed frame shifting, proteasome-independent degradation, control by *e.g.* c-Myc, NQO1, APC, and an internal ribosome entry site (IRES), to name just a few.[147–150] Ornithine, derived from arginine in the urea cycle, is expressed primarily in the liver and intestine, while polyamines are made in all tissues and are present in cheese and red meat. Spermidine synthase and spermine synthase use dcSAM to convert putrescine to spermidine, and spermidine to spermine, respectively, while fusion of the methionine backbone of dcSAM to putrescine generates methylthioadenosine (MTA), which can be recycled to methionine.[88,151] Both methylation and polyamine levels decline during life, instigating early trials to prevent age-related senescence and/or cancer.[138,152,153]