methyltransferases can either activate or further repress transcription, depending on the amino acid being methylated and the presence of other methyl or acetyl groups in the vicinity.[87]

4.1 INHIBITORS OF HISTONE METHYLTRANSFERASES

Several proteins are able to catalyze the addition of methyl groups to lysine or arginine residues of histones using *S*-adenosylmethionine (SAM) as the methyl donor (Figure 8.20).

Specific lysines in H3 and H4 histones can be mono-, di-, or trimethylated, whereas arginines can be monomethylated, asymmetrically dimethylated, or symmetrically dimethylated (Figure 8.21).

Although histone methylation does not alter the positive charge of the amino groups, several reader proteins specifically recognize this transformation and recruit additional enzymes whose activity may alter the local chromatin environment, thus affecting transcription. Consequently, activating or inactivating mutations, as well as overexpression of specific methyltransferases, can result in disease development.

The fact that histone lysine methylation is a much slower process than histone lysine acetylation (a half-life of 0.3–4 days compared to 2–40 min for histone acetylation) has led to the suggestion that methylation could impose memory on gene transcription and could be a potential example of heritable epigenetic control.

Among histone lysine *N*-methyltransferases, overexpression of EZH2, which mediates histone H3K27 trimethylation,[88] has been found in various cancers, and its inhibition is associated with gene silencing. This enzyme is coordinately expressed and functions upstream of the histone methyl transferase MMSET, which mediates H3K36 dimethylation. The discovery of 3-deazaneplanocin A (DZNep) as an inhibitor of EZH2 opened the possibility to pharmacologic inhibition of histone methylation[89] and the identification of HZH2–MMSET axis as an attractive therapeutic target in cancer.[90] BIX 01294, another inhibitor of MMSET, is a promising preclinical candidate for the treatment of some patients with multiple myeloma because this enzyme is overexpressed in myelomas with the translocation t(4,14).[91] Mithramycin A (aureolic acid, plicamycin, Mithracin®) is a natural antibiotic that, through binding to GC-rich regions in DNA, prevents the approach of HMTs, causing the DNA to coil up and be inaccessible for transcription. Mithramycin A is also a strong activator of the tumor suppressor p53 protein in human hepatoma cells,[92] being used for the treatment of patients with Paget's disease of bone as well as for several other forms of cancer.

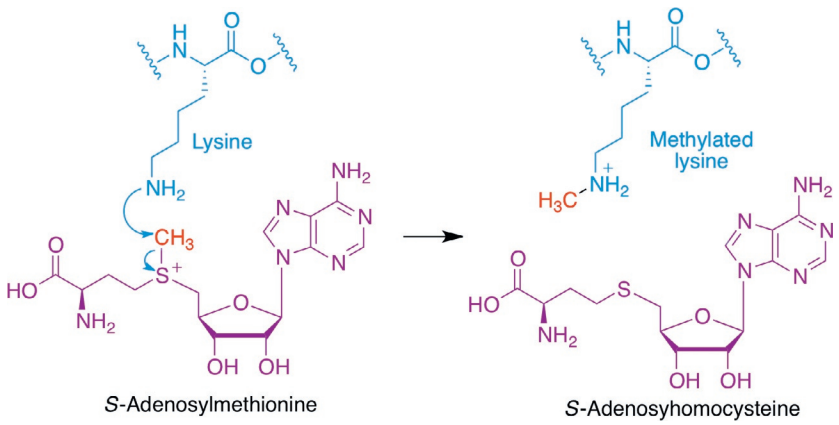

FIGURE 8.20

Mechanism of lysine methylation.