4.2 LYSINE-SPECIFIC DEMETHYLASES (LSDs OR KDMs) AND THEIR INHIBITORS

Some years ago, histone methylation was believed to be a stable modification that was only erased upon histone exchange or during DNA replication, but this idea was rejected following the demonstration that lysine-specific demethylase 1 (LSD1) catalyzes the demethylation of H3K4me1 and H3K4me2. Today, histone lysine demethylases are regarded as a specific group of eraser proteins that are implicated in the epigenetic control of cellular differentiation and in the development and maintenance of cancer, with the strongest biological evidence obtained for the LSD1, JARID1B, FBXL10, and JMJD2 families.

Lysine-specific demethylases LSD1[93] and LSD2, also known as KDMs, have an amine oxidase-like (AOL) domain and a chromatin factor-associated SWIRM domain. The SWIRM domain is thought to participate in protein–protein interactions rather than in protein–DNA interactions, which may explain the ability of LSDs to recognize different substrates. The AOL domain displays two subdomains, one that binds to the cofactor FAD and another that binds to the substrate, whose interface forms the catalytic center. Lysine demethylation catalyzed by these enzymes is likely to occur through the hydride transfer mechanism showed in Figure 8.22.[94]

The catalytic domains of the LSD proteins share sequence homology with monoaminooxidases MAO-A and MAO-B, which are responsible for the oxidative deamination of dopamine and serotonin, respectively. Accordingly, a few inhibitors of these enzymes, most notably tranylcypromine (a mechanism-based inhibitor that forms a covalent adduct with the FAD cofactor in the AOL domain), also inhibit LSD1, presumably via the same mechanism (Figure 8.23).[95]

To avoid the adverse effects of nonselective amine oxidase inhibitors, several derivatives of tranylcypromine with enhanced potency and target selectivity for LSD1 have been obtained through modification of the phenyl and the amino groups, and some of these derivatives have proved to be potent and selective LSD1 inhibitors.[96]

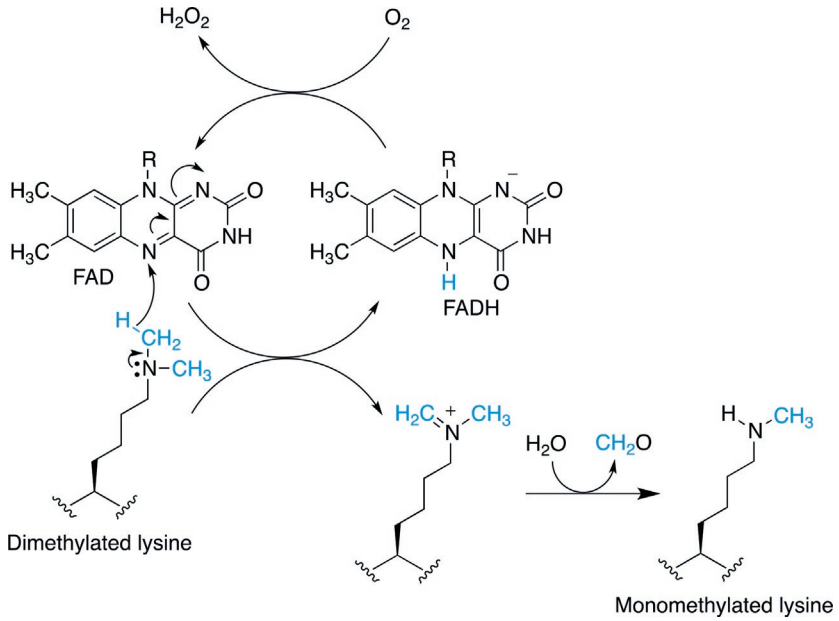

FIGURE 8.22

Mechanism of lysine demethylation by LSDs (KDMs).