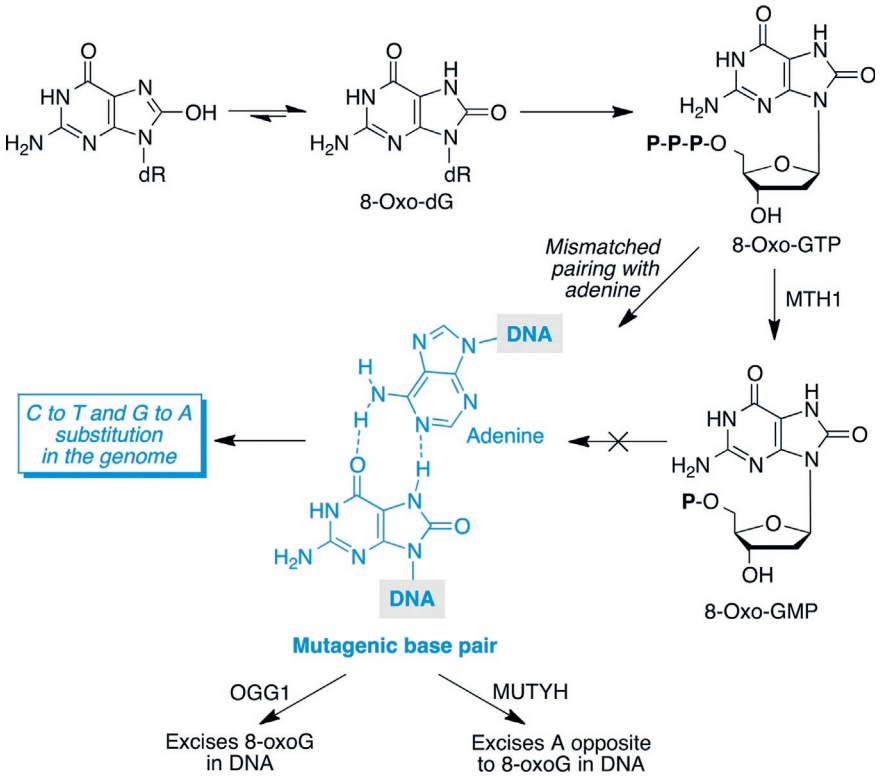

FIGURE 4.14

Defense against oxidative damage of nucleic acids by the MTH1 protein.

and thus minimizes the accumulation of 8-oxoG in the cellular genomes. MUTYH is an adenine/2-hydroxyadenine DNA glycosylase that excises adenine opposite 8-oxoG and thus suppresses 8-oxoG-induced mutagenesis (see Figure 4.14). An increased susceptibility to spontaneous carcinogenesis in MTH1-, OGG1-, and MUTYH-deficient mice has been observed.[18]

These defense mechanisms also play an important role in neuroprotection. 8-Oxoguanine is accumulated in nuclear and mitochondrial genomes during aging, and it increases dramatically in nigrostriatal dopaminergic neurons of patients with Parkinson's disease (PD), showing that oxidative damage in nucleic acids is a major risk factor for PD.[19]

These enzymes play important roles in mammalian cells, avoiding an accumulation of oxidative DNA damage, in both nuclear and mitochondrial genomes, and thereby suppressing carcinogenesis and cell death. Nevertheless, they can be regarded as nonessential in normal cells that have a regulated metabolism preventing damage of nucleotide building blocks, whereas some cancer cells require them for survival due to their altered metabolism. In this context, MTH1 has been recently validated as an anticancer target.[20] Interestingly, (*S*)-crizotinib (Xalkori®), an anticancer drug acting as an ALK (anaplastic lymphoma kinase) and ROS1 (c-ros oncogene 1) inhibitor that is discussed in Section 4.10 of Chapter 10, has been shown to be a nanomolar inhibitor of MTH1.[21] Some additional small molecules,