The DR pathway restricts the therapeutic response of tumors to chloroethylating or methylating agents through the repair factor O^6-alkylguanine DNA alkyltransferase (AGT).[110] The BER pathway reduces tumor sensitivity to alkylating or oxidative agents by repairing oxidized-reduced, alkylated, or deaminated bases through multiple enzymes that include DNA glycosylases, which remove the damaged base generating an apurinic–apyrimidic (AP) site; apurinic–apyrimidinic endonuclease 1 (APE-1), which cleaves the phosphodiester bonds at the 5′ end of the AP site; and Polβ, which is recruited to fill this gap with assistance from PAR and PARP1. The HR and NHEJ pathways repair DSBs produced after the use of ionizing radiation or the administration of alkylating agents, topoisomerase inhibitors, or drugs that generate ROS. The targets of these two DNA repair pathways are ATM (ataxia–telangiectasia mutated) and DNA-PKcs (DNA-dependent protein kinase catalytic subunit), respectively.

4.1 INHIBITORS OF O^6-ALKYLGUANINE DNA ALKYLTRANSFERASE (MGMT OR AGT)

As discussed in Chapter 5, DNA damage by several types of alkylating agents, such as nitrosoureas and temozolomide, is initiated by alkylation of the guanine O^6 atom. This damage is repaired by O^6-alkylguanine DNA alkyltransferase (AGT), also known as O^6-methylguanine DNA methyltransferase (MGMT), which covalently transfers the guanine O^6-alkyl group of alkylated DNA to the enzyme cysteine residue Cys-145 in its active site before mispairing of bases or covalent cross-links can occur (Figure 14.16). This reaction is stoichiometric in terms of MGMT, which is deactivated. Therefore, MGMT may be considered as a sacrificial or suicide enzyme and an interesting anticancer target for combination therapy, because its inhibition potentiates the antitumor effect of those alkylating agents for which O^6-alkylation is the determinant of cancer cell death,[111] especially carmustune and temozolamide.[112] However, it must be remembered that alkylating agents also react at other DNA positions, especially guanine N-7 and adenine N-3, a damage that is repaired by the base excision repair system.

The main type of MGMT inhibitors are O^6-alkylguanine derivatives[113] that act as competitive inhibitors by analogy with the natural substrate and inactivate the enzyme by transferring their O^6-alkyl

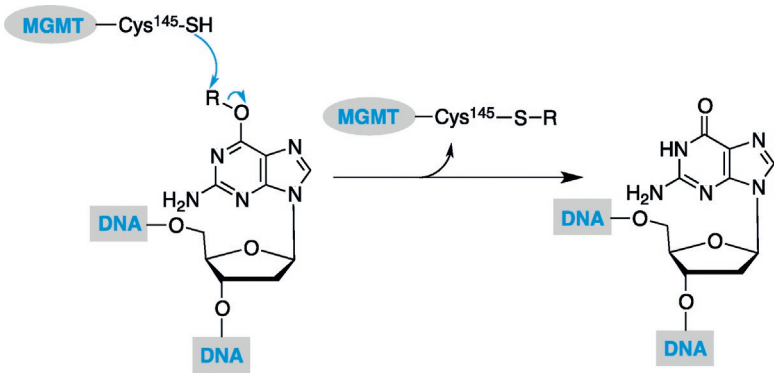

FIGURE 14.16

Repair of O^6-alkylguanine residues by alkylguanine transferase (MGMT).