polymerase (PARP) makes tumor cells more sensitive to base lesions and single-stranded breaks produced by ionizing radiation or alkylating drugs; inhibitors of components of double-strand DNA breaks (DSBs) repair mechanisms, such as homologous recombination (HR) or nonhomologous end-joining (NHEJ), are radiosensitizers; inhibitors of O^6-methylguanine DNA methyltransferase (MGMT) sensitize cancer cells to alkylating agents; and inactivators of components of the nucleotide excision repair (NER) make cells more sensitive to cisplatin and similar chemotherapeutic drugs.

The vast knowledge that has been obtained about resistance mechanisms has not yet resulted in the expected clinic advances to improve diagnostic assays, predict individual therapy responses, or develop effective chemo- or radiosensitizers to enhance the efficiency of the therapy.[6] In this chapter, the main intratumor and extratumor processes that are involved in the development of radio- and chemoresistance are discussed, omitting the previously mentioned role of cancer stem cells (see Chapter 11, Section 7).

2 ABC EFFLUX PUMPS IN ANTICANCER DRUG RESISTANCE

Multidrug transporters are present in almost all cells to protect them from xenobiotics through an active excretion mechanism. The multidrug resistance (MDR) phenotype is mostly associated with the overexpression of P-glycoprotein (Pgp) and of multidrug resistance-associated protein-1 (MRP1). Both proteins are members of the superfamily of membrane transport carriers known as ATP-binding cassette (ABC) proteins, which hydrolyze ATP as an energy source to drive the outwardly directed transport of substrates against a concentration gradient and therefore reduce their intracellular concentration.[7] To date, most studied compounds that reverse this event, which are known as MDR modulators, resistance modifiers, or chemosensitizers, are Pgp inhibitors. Three generations of these inhibitors have enhanced the understanding of the mechanisms involved in chemotherapy resistance, but their clinical success has been limited and none of them have reached the market.

2.1 GENERAL FEATURES OF ABC EFFLUX PUMPS

ABC transporters are membrane "pump" proteins that eliminate toxic chemicals present in organs related to digestion and excretion, such as the biological membranes of the intestinal wall. The genes responsible for their synthesis are activated by environmental stress (e.g., by foreign chemicals or heat). These transporters have great importance in drug absorption and, through the removal of drugs from the cells, are the major cause for failure of anticancer chemotherapy (Figure 14.1a). Consequently, much effort has been placed in the development of blockers of these transport proteins in order to restore the sensitivity of the cell to the anticancer drug (Figure 14.1b).[8]

ABC proteins are organized similarly and contain transmembrane domains, which contain 5–10 membrane-spanning R-helices where the substrate binding sites are located and nucleotide-binding domains (NBDs) with ATPase activity that provides energy to allow the transport process. The structures of three representative types of ABC transporters involved in resistance to anticancer agents are shown in Figure 14.2.

Pgp is a membrane-associated 170-kDa glycoprotein that effluxes approximately 50% of all anticancer agents used clinically today without chemically modifying them. It is overexpressed in many