2 Combinations of Antimetabolites and Ionizing Radiation

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2.1 Antimetabolites: Classes, Intracellular Metabolism, and Mechanisms of Action

Antimetabolites have antineoplastic activity, which is attributed to the fact that their structure is very similar to the normal metabolites required for cell function and replication. After intracellular modification, the antimetabolites interact with intracellular enzymes and show cytotoxic effects by (a) substituting for a normal metabolite incorporated into key molecules, such as DNA and RNA, and (b) occupying the catalytic site of a key enzyme and competing with a normal metabolite. Consequently, they interfere with DNA synthesis and proliferation of the cancer cell. Until recently, several kinds of antimetabolites have been developed and are categorized into three major groups, pyrimidine analogs (see Fig. 2.1a), folic acid analogs (see Fig. 2.1b) and purine analogs (see Fig. 2.1c). The mechanisms of action of representative agents in each class are briefly described herein.

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2.1.1 Pyrimidine Analogs

2.1.1.1 5-Fluorouracil

5-Fluorouracil (5-FU) is a nucleoside analog of uracil in which a fluorine atom is inserted into the C-5 position in place of hydrogen (see Fig. 2.1a; Longley et al. 2003). It has been widely applied for the treatment of various kinds of cancers, particularly for colorectal and breast cancers. 5-FU requires metabolic activation to form its cytotoxic metabolites (see Fig. 2.2; Malet-Martino and Martino 2002; Longley et al. 2003). 5-FU is converted to 5-fluorouridine-5'-monophosphate (5-FUMP) directly by orotate phosphoribosyltransferase (OPRT) or indirectly via an intermediate metabolite, 5-fluorouridine (5-FUrd), by uridine phosphorylase and uridine kinase. 5-FUMP is subsequently phosphorylated to 5-fluorouridine-5'-diphosphate (5-FUDP) by pyrimidine monophosphate kinase and further to a cytotoxic metabolite, 5-fluorouridine-5'-triphosphate (5-FUTP) by pyrimidine diphosphate kinase. The 5-FUTP can mimic uridine-5'-triphosphate (UTP), and be recognized by RNA polymerases as the substrate. This leads to the incorporation of 5-FU in all classes of RNA, disrupting normal RNA func-

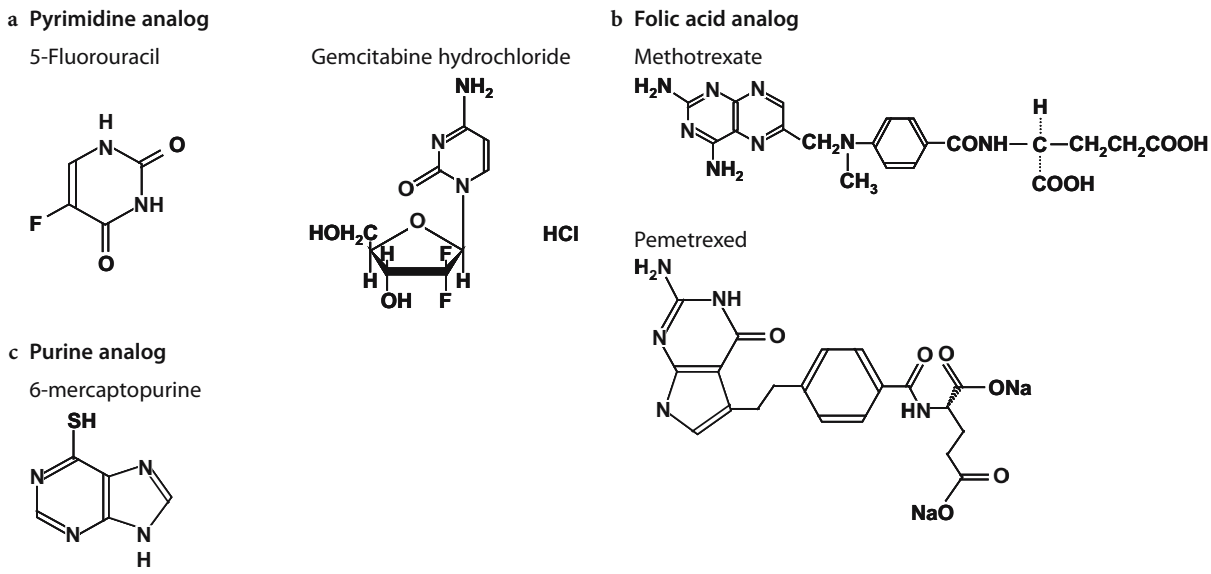

Fig. 2.1a-c. Structures of antimetabolites. **a** Pyrimidine analogs, gemcitabine hydrochloride, and 5-fluorouracil. **b** Folic acid analogs, methotrexate and pemetrexed. **c** Purine analog, 6-mercaptopurine

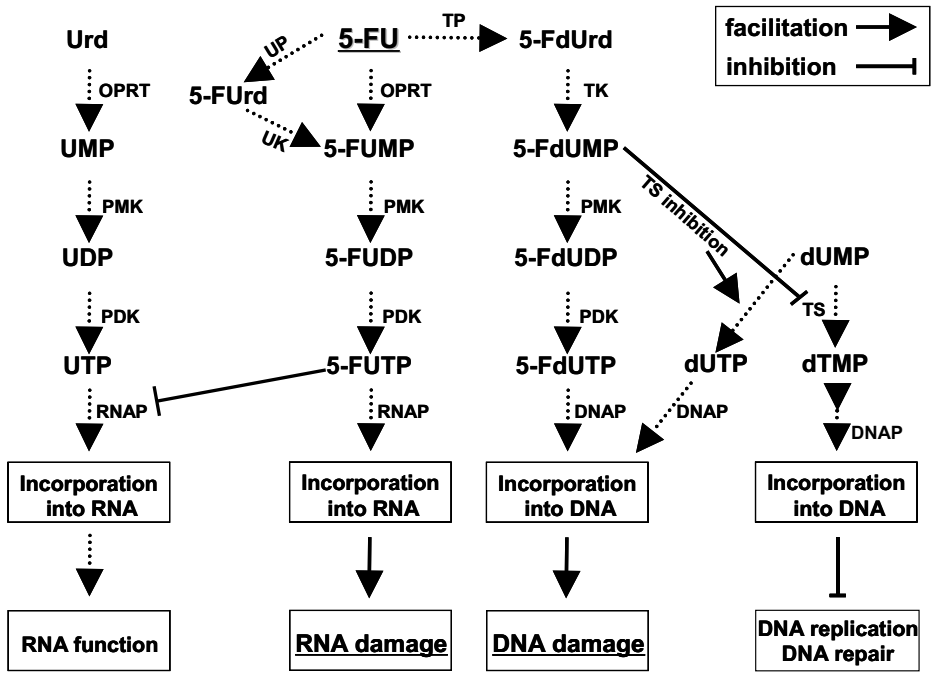

Fig. 2.2. Metabolism and mechanism of action of 5-fluorouracil. 5-fluorouracil (5-FU), 5-fluorouridine-5'-monophosphate (5-FUMP), orotate phosphoribosyltransferase (OPRT), 5-fluorouridine (5-FUrd), uridine phosphorylase (UP), uridine kinase (UK), 5-fluorouridine-5'-diphosphate (5-FUDP), pyrimidine monophosphate kinase (PMK), 5-fluorouridine-5'-triphosphate (5-FUTP), pyrimidine diphosphate kinase (PDK), RNA polymerase (RNAP), uridine (Urd), Uridine-5'-monophosphate (UMP), uridine-5'-diphosphate (UDP), uridine-5'-triphosphate (UTP), 5-fluoro-2'-deoxyuridine (5-FdUrd), thymidine kinase (TK), 5-fluoro-2'-deoxyuridine-5'-monophosphate (5-FdUMP), 5-fluoro-2'-deoxyuridine-5'-diphosphate (5-FdUDP), 5-fluoro-2'-deoxyuridine-5'-triphosphate (5-FdUTP), thymidylate synthase (TS), thymidine-5'-monophosphate (dTMP), 2'-deoxyuridine-5'-monophosphate (dUMP), thymidine-5'-triphosphate (dTTP), 2'-deoxyuridine-5'-triphosphate (dUTP), DNA polymerase (DNAP)