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DNA-damage sensitizers: Potential new therapeutical tools to improve chemotherapy

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Abstract

Agents that induce DNA damage in cells – the so-called genotoxins – have successfully been used for decades to treat patients with tumors. Genotoxins alter the DNA of cells, which is detected by DNA damage sensors and which leads to the activation of p53. Activation of p53 can lead to the death of cancer cells. The efficacy of genotoxins in humans is however limited by their toxicity to normal tissues. Specific sensitization of tumor cells to the action of genotoxins would reduce the efficacious doses of genotoxins to be used in patients, diminishing the detrimental side-effects of the drugs on normal tissues. A series of compounds able to sensitize cancer cells to DNA-damaging drugs have recently been identified that have the potential to increase the efficacy of currently used anti-cancer treatments.

Keywords: Chemotherapy; Genotoxins; DNA damage; Cancer; Sensitizers; p53

Anti-cancer agents that target the DNA (genotoxins) are among the most used compounds to fight tumors. Unfortunately, genotoxins can induce severe side-effects in patients as they can also damage healthy tissues. Consequently, one of the current efforts in oncology is to find agents that can

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Table 1
Mode of action and clinical use of genotoxins

Drugs	Mechanism of action	Used against
5-Fluorouracil	Thymidilate synthase inhibitor	Basal cell carcinoma; breast cancer; cervical cancer; colorectal cancer; head/neck cancer; pancreatic cancer; stomach cancer
Chlorambucil	Inter-strand DNA cross-linker	Chronic lymphocytic leukemia; malignant lymphomas
Cisplatin	Intra-strand DNA cross-linker	Metastatic testicular cancer; ovarian cancer; head/neck cancer; breast cancer; Hodgkin's and non-Hodgkin's lymphoma; myeloma and melanoma
Cyclophosphamide	Inter-strand DNA cross-linker	Breast cancer; leukemias; lymphoma; multiple myeloma; neuroblastoma; ovarian cancer; retinoblastoma
Doxorubicin	Topoisomerase II inhibitor	Leukemias; Wilms' tumor; neuroblastoma; soft tissue and bone sarcomas; small cell carcinoma of the lung; lymphomas; multiple myeloma; mesotheliomas; germ cell tumors of the ovary or testis
Etoposide	Topoisomerase II inhibitor	Acute leukemia; adrenal cortical cancer; brain cancer; chronic lymphocytic leukemia; choriocarcinoma; esophageal cancer; Ewing's sarcoma; gastric cancer; germ cell cancer; hepatocellular cancer
Irinotecan	Topoisomerase I inhibitor	Cervical cancer; colorectal cancer; esophageal cancer; gastric cancer; non-small cell lung cancer; small cell lung cancer
Methotrexate	Dihydrofolate reductase inhibitor	Bladder cancer; breast cancer; esophageal cancer; head/neck cancer; leukemia; lymphoma; lung cancer; osteosarcoma
Topotecan	Topoisomerase I inhibitor	Small cell lung carcinoma; cervical cancer

increase the potency of genotoxins specifically in cancer cells so that the efficacious doses of genotoxins can be lowered to reduce deleterious side-effects or, if the side-effects are not too problematic, to increase the killing efficiency of the genotoxins. Such agents, called sensitizers, are the focus of the present review. In the first part, the basic principles underlying the anti-tumor activities of genotoxins will be introduced. The second part will deal with agents that have been shown to function as genotoxin sensitizers.

1. DNA damage mediates the apoptosis-inducing properties of genotoxins

The beginnings of the modern era of chemotherapy can be traced to the discovery by Goodman and Gilman that nitrogen mustard injected into the bloodstream of a patient with advanced non-Hodgkin's lymphoma led to tumor regression [1]. When this discovery was made, the mechanisms inducing tumor regression were not known but later studies showed that nitrogen mustard was able to interact covalently with DNA and the consequence of this interaction was induction of apoptosis [1]. The discovery that chemical agents interacting with DNA or inducing DNA damage were able to block the progression of cancers opened new research and led to the discovery of many molecules that are still used today (Table 1). These so-called genotoxins are often alkylating agents that interact directly with DNA, generating intra- or inter-strand cross-links. These modifications interfere with DNA replication and transcription, two essential cellular processes whose disruption induces apoptosis. Some of the genotoxin agents do not interfere directly with DNA but rather interact and inhibit proteins essential for DNA synthesis (e.g. dihydrofolate reductase) or proteins responsible for DNA topology maintenance (e.g. topoisomerases). The inhibition of these proteins also leads to DNA damages and disruption of DNA replication and protein synthesis (Fig. 1).

It has been shown that cells treated with DNA-damaging drugs can also die via necrosis, a form of non-programmed cell death [2]. Moreover, even though it is assumed that the primary target of genotoxins is DNA, genotoxins may also alter other cellular components such as RNA and proteins [3]

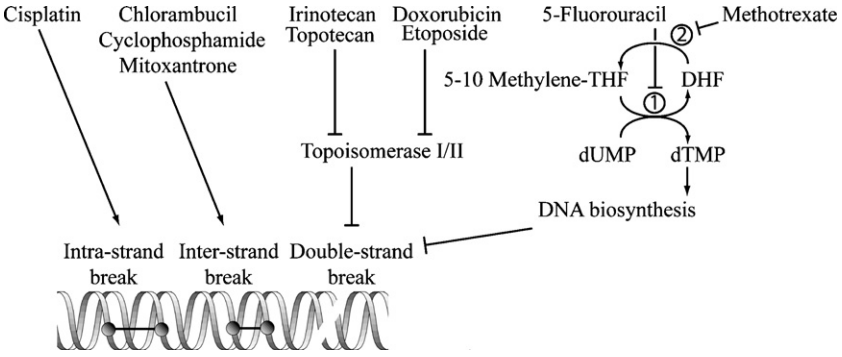

Fig. 1. Molecular interactions of genotoxins with DNA. The types of modifications induced by the indicated drugs include cross-linking, intercalation, and DNA-strand cleavage. These modifications are induced directly or arise from the repression of key proteins in the regulation of DNA synthesis or DNA topology. (1) Thymidylate synthase and (2) dihydrofolate reductase. *Abbreviations*: 5–10 Methylene THF, 5–10 methylene tetrahydrofolate; DHF, dihydrofolate.