Chapter 16

USING YEAST TOOLS TO DISSECT THE ACTION OF ANTICANCER DRUGS:
MECHANISMS OF ENZYME INHIBITION AND CELL KILLING BY AGENTS TARGETING DNA TOPOISOMERASES

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1 INTRODUCTION

Resistance to anticancer agents is one of the defining problems of cancer pharmacology. Drug resistance is clearly a major obstacle to the cure of many neoplastic diseases. Through the years we have come to understand that anticancer drug resistance has different biochemical and molecular mechanisms depending on the class of drug. Early studies centered on trying to understand “acquired drug resistance”, alterations in cancer cells that were originally sensitive to one or more chemotherapeutic agents, but which acquired changes that attenuated the cell cytotoxicity of the original agent, and also frequently resulted in “multidrug resistance”, resistance to multiple classes of anticancer agents. While prevention of acquired drug resistance, and a detailed understanding of mechanisms leading to drug resistance are still critical concerns of cancer pharmacology, we now understand that many cancer cells accumulate changes that result in inherent drug resistance. Alternatively, some of the changes leading to the development of neoplastic disease can make cancer cells inherently more sensitive to specific classes of anticancer agents. Current experimental approaches are providing a detailed description of the molecular changes that occur in many types of cancers.
One approach to converting this description of the molecular changes that occur in cancer into effective therapeutic strategies entails the design of new agents that specifically inhibit the proteins that have become essential for the survival and proliferation of cancer cells. A second approach is to optimize drugs acting against established anticancer targets. Both approaches require a detailed understanding of how anticancer drugs can lead to cell death, starting with a precise understanding of the target(s) of a drug, the cellular process affected by drug action, and the consequences of target inhibition.

DNA topoisomerases are an important target of many clinically active anticancer agents. Both type I and type II topoisomerases are targeted by various anticancer drugs. Type I topoisomerases are targeted by the camptothecins, which have demonstrated substantial clinical activity in a wide range of tumors. Topoisomerase II is the target of many chemically diverse agents including epipodophyllotoxins such as etoposide [74] and anthracyclines such as doxorubicin [64]. While these agents have substantial antitumor activity, a wide range of questions remains to be answered. For example, while it is well established that drugs such as etoposide target topoisomerase II, the biochemical mechanisms leading to enzyme inhibition remain to be identified. This is an important issue for topoisomerase II-targeting agents such as mAMSA that have been clinically disappointing. While many properties of a drug can influence its clinical activity, differences in biochemical mechanisms of drugs affecting the same target may be of decisive importance. Since drugs targeting topoisomerases are typically used in combination with drugs affecting other targets, a comprehensive understanding of cell-killing mechanisms is an important tool for devising optimal multidrug schedules. Finally, as is the case for most types of cytotoxic chemotherapy, drugs targeting topoisomerases can lead to a wide range of undesirable side effects. For topoisomerase II-targeting drugs, this includes the induction of translocations that can cause secondary malignancies [38].

Yeast has been a powerful model system for studying both the biological roles of DNA topoisomerases, and for studying the mechanism of action of drugs targeting these enzymes [41, 42]. Since topoisomerases play roles in so many different DNA transactions, higher eukaryotes do not readily tolerate mutations that impair topoisomerase activity. By contrast, introduction of defined topoisomerase alterations has proven to be a productive approach to understanding topoisomerase biology as well as drug action. This review concentrates on using yeast to study antitopoisomerase drug action. Several recent reviews have provided a detailed description of the roles of topoisomerases in different biological processes [41, 42, 71].