Molecular Mechanisms of Anthracycline Activity

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Abstract On the basis of evidence that anthracyclines are DNA intercalating agents and DNA is the primary target, a large number of analogs and related intercalators have been developed. However, doxorubicin and closely related anthracyclines still remain among the most effective antitumor agents. Multiple mechanisms have been proposed to explain their efficacy. They include inhibition of DNA-dependent functions, free radical formation, and membrane interactions. The primary mechanism of action is now ascribed to drug interference with the function of DNA topoisomerase II. The stabilization of the topoisomerase-mediated cleavable complex results in a specific type of DNA damage (i.e., double-strand protein-associated DNA breaks). The drug-stabilized cleavable complex is a potentially reversible molecular event and its persistence, as a consequence of strong DNA binding, may be recognized as an apoptotic stimulus. Indirect evidence supports the notion that the bioreductive processes of the quinone moiety generating the semiquinone radical with concomitant production of reactive oxygen species may contribute to the drug effects. The cellular defense mechanisms and response to genotoxic/cytotoxic stress appear to be critical determinants of the tumor sensitivity to anthracyclines.

Keywords Anthracyclines · Cellular resistance · Cleavable complex · DNA damage · Topoisomerase II

Abbreviations
BCRP Breast cancer resistant protein
BSO Buthionine sulfoximine
GSH Glutathione
LRP Lung resistant protein
Introduction

Anthracyclines represent a major class of antitumor antibiotics. The most effective member, doxorubicin, is one of the most widely used antitumor agents because of its broad spectrum of antitumor activity. The clinical success of daunorubicin and doxorubicin, the first generation of anthracyclines, has stimulated an intensive effort in the synthesis of analogs or structurally related compounds [1]. In spite of the preclinical development of a large number of agents of this class, only a small number of anthracyclines or related DNA intercalating agents are available for clinical use.

The basic structure of anthracyclines consists of a tetracyclic aglycone linked to an amino sugar (Fig. 1). In an attempt to improve the therapeu-