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Mutagenic and Cytotoxic Effects of Doxorubicin (Adriamycin) and Epeirubicin, Common Anthracycline DNA II Topoisomerase Inhibitors Used Against Breast Cancer, in Prokaryotic and Eukaryotic Cells

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For more than 40 years, anthracyclines have represented one of the most commonly used anticancer drugs. Doxorubicin and epirubicin are the morst common chemicals used against breast cancer, It is known that anthracyclines interact with the DNA double helix in a variety of very complex manners, which include intercalation of doxorubicin into the DNA duplex, formation of formaldehyde-mediated DNA crosslinks (primarily between neighboring guanines), and the catalytic inhibition of DNA topoisomerse II. Numerous studies in our lab have shown that four anthracyclines (daunorubicin, idarubicin, doxorubicin, and epirubicin) can induce DNA base excision repair and O6 alkylguanine DNA repair alkyltransferase- dependent base-substitution events and frameshift mutaions in the bacterium Salmonella typhimurium. More recent studies evaluated the recombinogenic potential of anthracyclines in a eukaryotic unicellular organism Saccharomyces cerevisiae. In the yeast deletion (DEL) assay, recombination is induced by the formation of DNA strand breaks, which are a substrate for initiation of genetic repair in this organism. Using the DEL assay, our lab has examined the role of DNA recombination pathways in the recognition and removal of anthracycline-induced DNA adducts. Specifically, doxorubicin (49.1 fold) and epirubicin (279 fold) tested positive in this assay. Our next step is to examine the pre-carcinogenic anthracycline-dependent events in mammals.

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