Characterization of an unique route to DNA strand breaks by DNA alkylating agents involving DNA alkylation, depurination, and the resulting AP sites

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Molecular damage caused by DNA-reactive carcinogens and anticancer drugs can lead to the formation of abasic sites, oxidative species, alkylation adducts, and DNA strand breaks. The relative contribution of these DNA lesions to the undesirable mutagenic or desirable therapeutic properties of alkylating agents is still undefined. Leinamycin is a very unusual natural compound that has many novel structural components, including a 1, 2-dithiolan-3-one 1-oxide moiety connected in a spiro fashion to an 18- membered lactam macrocycle coupled with a thiazole ring. This compound is capable of forming guanine adducts (N7) in DNA that are converted into abasic sites and simultaneously generate reactive oxygen species (ROS) to produce DNA strand breaks in mammalian cells. In our study, using leinamycin as a model compound, we characterized possible chemical events that could lead to the formation of DNA strand breaks by DNA alkylating agents involving DNA alkylation, depurination, and the resulting AP sites. In accordance with chemical and biochemical events, we observed that this alkylating agent indeed increases the number of AP sites, forms DNA strand breaks, and produces ROS inside human cancer cell lines, establishing a strong link between the DNA-damaging properties of leinamycin and its biological activity. Taken together, the results of our study present a new chemical or biochemical route that can explain the potent therapeutic or undesirable cytotoxic activity of DNA-reactive carcinogens and anticancer drugs against mammalian cells.

Biography

Daekyu Sun completed his Ph.D. and postdoctoral training at the College of Pharmacy at the University of Texas at Austin. He was employed with the Cancer Therapy Research Center (CTRC) at San Antonio, Texas from 1995 to 2002 as a Research Scientist and Assistant Member. He has been employed as an Assistant Professor at the University of Arizona at Tucson, Arizona since 2008. He has published more than 64 papers and has served as a reviewer for several reputed journals, such as the Journal of Nucleic Acids and Journal of Medicinal Chemistry.

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