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Application of mass spectrometry in the discovery of small molecule inhibitors of DNA repair proteins as potential anticancer drugs

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Most therapeutic agents kill tumor cells by damaging DNA. Evidence shows that cancer cells increase their capacity to repair DNA by overexpressing DNA repair proteins. Increased DNA repair that may remove DNA lesions before they become toxic to cancer cells is a major mechanism for the development of resistance to therapy. DNA repair proteins constitute targets for inhibitors to overcome the therapy resistance. Inhibition of DNA repair proteins may help selectively kill cancer cells in combination therapy or monotherapy. Among DNA repair proteins, DNA glycosylases remove modified DNA bases in the first step of the base excision repair mechanism, paving the way for other proteins to fully repair DNA. We planned experiments to discover small molecule inhibitors of human DNA glycosylases NEIL1, OGG1 and NTH1. First, a fluorescence-based assay was developed to detect both glycosylase and lyase activities of these proteins. From a primary screen of ′ 400,000 compunds, a number of inhibitors were identified. We applied GC-MS/MS with isotope dilution to determine the inhibition of NEIL1, OGG1 and NTH1 by identifying and quantifying the excised levels of their substrates. Four purine analogs were found to be potent inhibitors of the excision of NEIL1 substrates. Three of the four NEIL1 inhibitors also inhibited the exicision of NTH1 substrates, but not those of OGG1. Five other inhibitors were found to be potent inhibitors of the excision of OGG1 substrates; however, they displayed no inhibition of NEIL1 and NTH1 activities. Overall, this work forms the foundation for future drug discovery for DNA glycosylases.

Biography

Dizdaroglu has obtained his PhD at the Karlsruhe Technical University, Germany, and subsequently worked for seven years at the Max-Planck-Institute for Radiation Chemistry, Germany, before moving to US in 1978. He has been at the National Institute of Standards and Technology (NIST) for more 30 years. In 2006, Dr. Dizdaroglu was conferred upon the rank of NIST Fellow. He published more than highly cited 230 papers. Dizdaroglu received numerous scientific awards including the Hillebrand Prize of the American Chemical Society and the Gold Medal Award of the US Department of Commerce. He was also awarded two Honorary Doctorates.

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