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### Measurement of DNA repair proteins in human tissues by liquid chromatography-tandem mass spectrometry with isotope-dilution

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Malignant tumors possess increased DNA repair capacity that may affect the therapy and outcome of cancer. Thus, DNA repair proteins are becoming predictive, prognostic and therapeutic factors in cancer. Accurate measurement of expression levels of these proteins in tumors and normal tissues will likely help develop and guide treatment strategies. We developed an approach involving LC-MS/MS with isotope-dilution to positively identify and accurately quantify several DNA repair proteins in human cells, including APE1 and MTH1. As a major endonuclease in mammals, APE1 is involved in base excision repair and possesses other functions. Evidence points to the predictive and prognostic value of APE1 expression and subcellular localization in human cancers. MTH1 sanitizes the nucleotide pool so that oxidatively modified 2'-deoxynucleoside triphosphates (dNTPs) cannot be used in DNA replication. Cancer cells require MTH1 to avoid incorporation of modified dNTPs resulting in DNA damage leading to apoptosis. We produced <sup>15</sup>N-labeled full-length human APE1 and MTH1 to be used as internal standards. Unlabeled and <sup>15</sup>N-labeled proteins were digested with trypsin and analyzed by LC-MS/MS. Numerous tryptic peptides of APE1 and MTH1 were identified by their mass spectra. Multiple-reaction monitoring was used to monitor characteristic mass transitions of peptides. Subsequently, APE1 and MTH1 were identified and quantified in cultured human cell lines, and in human normal and cancerous breast tissues. Overexpression and subcellular de-localization in cancer cell lines and breast cancer tissues were observed. The novel approach developed in this work may help elucidate the role of APE1 and MTH1 in disease development and treatment responses.

#### Biography

Miral 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 than 30 years. In 2006, he was conferred upon the rank of NIST Fellow. He published more than highly cited 230 papers. He 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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