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The application of GC-MS/MS in the field of DNA damage and repair

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DNA damage occurs in living organisms by exogenous and endogenous sources. Unless repaired, DNA damage can cause genomic instability that may give rise to disease processes including carcinogenesis. Cancer tissues overexpress DNA repair proteins, leading to therapy resistance. Evidence suggests that DNA repair capacity may be a predictive biomarker of patient response. Thus, accurate measurement of DNA repair proteins in disease-free tissues and malignant tumors of patients may be essential in cancers, and for the development and use of inhibitors of these proteins in cancer therapy, and for determining the response of patients. We developed methodologies involving liquid chromatography-tandem mass spectrometry (LC-MS/MS) with isotope-dilution to positively identify and accurately quantify DNA repair proteins in human tissues. For this purpose, we produced and purified full length 15N-labeled analogs of human DNA repair proteins as internal standards. Following trypsin digestion, we identified numerous tryptic peptides of both unlabeled and 15N-labeled proteins by their full scan and product ion spectra. Next, we identified and quantified several DNA repair proteins in various human cultured cell lines, and in human disease-free breast tissues and malignant breast tumors. Extreme expression of the proteins in cancer cells and in malignant breast tumors was observed, suggesting that cancer cells may overexpress DNA repair proteins for survival. The approach described is expected to be applicable to the measurement of expression levels of DNA repair proteins in malignant tumors vs. surrounding disease-free tissues in patients. This attribute may help develop novel treatment strategies and DNA repair inhibitors as potential anticancer drugs, and guide therapies.

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