Alexei G Basnakian, J Clinic Toxicol 2016, 6:5(Suppl)
http://dx.doi.org/10.4172/2161-0495.C1.017

6th Global Summit on
Toxicology & Applied Pharmacology
October 17-19, 2016 Houston, USA

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Enzymatic DNA fragmentation: The mechanism and marker of drug toxicity

DNA is the longest polymer and the only cellular molecule that cannot be resynthesized if destroyed. The destruction of DNA beyond DNA repair capacity is provided by DNA endonucleases and causes the termination of DNA and mRNA syntheses. Since DNA destruction occurs immediately prior and after cell death, the endonucleases do not need to be induced to provide DNA fragmentation. Independently of cell death cause and mechanism, the endonuclease-mediated DNA fragmentation is the universal marker of irreversible cell death. Most active cellular DNA-fragmenting endonucleases are DNase I and Endonuclease G (EndoG). We studied whether overexpression of these two endonucleases would cause DNA fragmentation (TUNEL) and cell death (LDH release) without and in the presence of anticancer drugs (cyclophosphamide, cisplatin, docetaxel, etoposide, or camptothecin). Our experiments showed that expression levels of the two endonucleases strongly correlated with drug sensitivity of breast cancer and prostate cancer cells. Invasive cancer cell lines usually did not express DNase I, and the level of EndoG expression correlated with the degree of dedifferentiation. Overexpression of the endonucleases was not very cytotoxic by itself but made the cancer cell lines more sensitive to the drugs, while silencing of the endonucleases partially protected them from the drug toxicities. Orthotopic EndoG-deficient prostate cancer xenografts were not sensitive to docetaxel, but became sensitive after overexpression of EndoG. Normal kidney cells and mouse kidneys in vivo were highly sensitive to cisplatin toxicity, which was mediated by the same endonucleases. Newly developed chemical inhibitors of DNase I and EndoG protected cancer and kidney cells from anticancer drugs. These observations indicate the importance of the endonucleases in cancer drug toxicities, and suggest potential benefits of using them as helper drugs for anticancer therapy and as targets for protecting normal tissues against drug toxicities.

Biography

Alexei G Basnakian received his PhD and DSc degrees from the Russian Academy of Medical Science, both in the field of DNA endonucleases. He had Post-doctoral trainings in Molecular Biology at the Harvard Medical School and in Toxicology/Cancer Research at the National Center for Toxicological Research. He is Professor in the Department of Pharmacology and Toxicology, and Director of the DNA Damage and Toxicology Core Center at the University of Arkansas for Medical Sciences, and Research Career Scientist at the Veteran's Hospital in Little Rock, Arkansas, USA. He is an author of more than 85 peer-reviewed papers and 12 reviews or book chapters. He is an Editorial Board Member of several biomedical journals, and a member of NIH and VA grant study sections. His research interests are in DNA endonucleases and DNA damage associated with toxicity, anti-cancer therapy, cell injury and cell death.

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