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Endonuclease delivery as a new anti-cancer therapy

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Malignancy and invasiveness of cancer cells were shown to be associated with the suppressed ability to develop apoptosis in response to chemotherapy. However, the role of apoptotic (cytotoxic) DNA endonucleases, the key enzymes in inducing irreversible cell death, and their regulation in invasive cancer cells are not clearly understood. We have evaluated the expression of two most abundant endonucleases, DNase I and EndoG, in human breast and prostate cancer cell lines. This evaluation showed that invasive breast cancer cells (HCC1143, HCC1954 and HCC1395) and prostate cancer cells (PC3) have no detectable expression of DNase I, and significantly decreased expression of EndoG compared to normal or non-invasive cancer cells. The absence of EndoG in breast or prostate cancer cells negatively correlated with the sensitivity to anticancer drugs, such as cisplatin, etoposide, camptothecin, and docetaxel. The decrease of EndoG expression is caused by hypermethylation of EndoG gene, while suppression of DNA methylation activated the gene and made cells susceptible to chemotherapy drugs. The silencing of EndoG using specific siRNA decreased the chemoresistance of the cells, while overexpression of EndoG increased it. Finally, the expression of EndoG in orthotopic prostate PC3 cell xenografts in mice increased sensitivity of the tumors to docetaxel. Our findings suggest that the absence of EndoG in invasive breast or prostate cancer cells causes their decreased sensitivity to apoptosis induced by chemotherapy, while the delivery of EndoG gene restores the sensitivity and allows effective chemotherapy.

Biography

Alexei Basnakian received his PhD and DSc degrees from the Russian Academy of Medical Science, both in the field of DNA endonucleases. He had postdoctoral trainings in molecular biology in Harvard Medical School and cancer research in the National Center for Toxicological Research. Dr. Basnakian 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. He is an author of more than 70 peer-reviewed papers. Dr. Basnakian's research interests are in DNA endonucleases and DNA damage associated with cell injury and cell death.

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