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DNase-mediated toxicity in normal and cancer cells

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Endogenous cellular DNases mediate almost all kinds of toxicity to normal and cancer cells, and DNA fragmentation produced by these enzymes makes cell death irreversible. The principal difference between normal and cancer cells is that normal cells express high levels of DNases, while cancer cells have low expression and activity of DNases. The latter is the part of protective mechanism against injury of cancer cells during their growth in a hostile environment. Our studies showed that expression of two most active and abundant DNases, DNase I and EndoG, is strongly suppressed in breast or prostate cancer cell lines, which make them insensitive 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 the chemotherapy drugs. The silencing of EndoG using specific siRNA decreased the chemoresistance of the cells, while overexpression of EndoG increased it. The expression of EndoG in orthotopic prostate PC3 cell xenografts in mice increased sensitivity of the tumors to docetaxel. Off-target toxic effect of anticancer drugs on normal tissues was also mediated by DNases in several models. Administration of cisplatin induced toxicity to kidneys, cyclophosphamide induced alopecia, and administration of cisplatin, vinblastin or doxorubicin were toxic to vascular endothelial cells. Importantly, in all of these cases, genetic knockout of chemical inhibition of endonucleases were protective to normal tissues. Therefore, activation of DNases in cancer tissues while inactivating them in normal tissues should be considered as viable approach in cancer therapy.

Recent Publications

1. Jang D S et al. (2015) Novel cytoprotective inhibitors for endonuclease G. DNA Cell Biol. 34(2):92-100.
2. Jang D S et al. (2015) Novel high throughput DNase I assay. J. Biomol. Screening. 20(2):202-211
3. Zhdanov D D et al. (2015) Regulation of apoptotic endonucleases by EndoG. DNA Cell Biol. 34(5):316-326.
4. Rogers L J et al. (2016) 2-amino-1-methyl-6-phenylimidazo(4,5-b) pyridine (PhIP) induces gene expression changes in JAK/STAT and MAPK pathways related to inflammation, diabetes and cancer. Nutr Metab. 13:54.
5. Fahmi T et al. (2017) Mechanism of Graphene-Induced Cell Toxicity and DNA damage: role of endonucleases. J. Appl. Tox. 37(11):1325-1332.

Biography

Alexei G Basnakian received his PhD and DSc Degrees from the Russian Academy of Medical Science, both in the field of DNases. He had Postdoctoral trainings in Molecular Biology at Harvard Medical School (USA), and in cancer research at the National Center for Toxicological Research. He is a 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, USA. He is the author of 85 peer-reviewed papers. His research interests lies in DNases and DNA fragmentation associated with cell injury and cell death.

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