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Protection of host tissues from chemotherapy or radiation induced injuries by inactivation of apoptotic endonucleases

Cancer chemotherapy aims at eliminating tumor cells while leaving normal host cells intact. However many molecular mechanisms employed to kill cancer cells are the same as in normal cells. One of the important mechanisms mediating various chemotherapy drugs and cellular radiosensitivity are apoptotic endonucleases, the enzymes which degrade DNA. They are usually downregulated in cancer cells, which makes them resistant to the hostile body environment and chemotherapy. Induction of endonucleases by chemotherapy promotes death of both cancer and normal cells. We hypothesized that inactivation or inhibition of endonucleases in normal tissues would protect them from apoptosis during anti-cancer chemotherapy or radiation therapy in cultured cells and rodents. Our first observation was that even without therapy, growth of diethylnitrosamine-induced liver tumors in rats or orthotopic prostate xenografts in mice induced endonuclease activity in surrounding tissues immediately adjacent to tumors. No increase of endonuclease activity was observed in other organs. However, administration of cisplatin induced toxicity to kidneys, administration of cyclophosphamide induced alopecia, administration of cisplatin, vinblastin or doxorubicin were toxic to vascular endothelial cells, and a total body gamma irradiation induced apoptosis in radiosensitive organs (bone marrow, spleen and intestine). Importantly, in all of these cases, genetic knockout of chemical inhibition of endonucleases were protective to normal tissues. Therefore, protection of host tissues from chemotherapy- or radiation-induced injuries by inactivation of apoptotic endonucleases should be considered as viable approach in cancer therapy.

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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