Broad range DNase inhibitors as new drugs for amelioration of toxic acute kidney failure

Deoxyribonucleases (DNases) universally induce irreversible cell death by fragmenting DNA in response to cell injury. Despite that most of the DNase (endonuclease) activity is used after cell death, a genetic inactivation of DNases provides protection of cells and tissues against DNA breaks induced by cytotoxic stimuli. Therefore, DNases act before the “point of no return” in cell death and can be potentially used as the therapeutic target for tissue protection against injury. However, inhibitors of DNases are not available. To identify DNase inhibitors, we have developed a high-throughput screening assay based on a proprietary fluorescent probe. This assay allowed the identification of several new inhibitors of deoxyribonuclease I (DNase I), which were also active against two other DNases, endonucleases G (EndoG) and deoxyribonuclease II (DNase II). The DNase inhibitors were able to significantly protect kidney tubular epithelial cells in vitro and mouse kidneys in vivo against acute cisplatin or glycerol (rhabdomyolysis) toxicity. The inhibitors showed no toxicity in vivo at therapeutic doses. These or similar drugs have a great potential for tissue protection against toxic kidney failure.

Biography

Alexei G Basnakian received his PhD and DSc degrees from the Russian Academy of Medical Science, both in the field of DNA-degrading enzymes. He had postdoctoral training in molecular biology at the Harvard Medical School and in toxicology/cancer research at the National Center for Toxicological Research/US Food and Drug Administration. He is a tenured professor at 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 Veterans Hospital in Little Rock, Arkansas, USA. He is an author of 86 peer-reviewed papers and 14 reviews or book chapters. He is an Editorial Board member of several biomedical journals and a member of NIH, AHA and VA grant study sections. His research interests are in DNases/endonucleases and DNA damage associated with toxicity, anti-cancer therapy, tissue injury and cell death.