Radioprotection of Normal Cells Using CD47 Morpholino Antisense Therapeutics Causes Progression of Prostate Cancer

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Irreparable DNA lesions caused by radiation therapy induce apoptosis, a suicidal response that occurs in both cancerous and normal cells. Remarkably, mouse and human tissues in experiments that use the oligonucleotide gene silencing technology CD47 morpholino antisense (MO) are able to survive and grow even after exposure to high dose ionizing radiation. However, the pathway by which this drug works has not been identified or if it differs between normal and cancerous cells. This project focused on finding the unknown mechanism of the MO. It was assumed that because the dual role of CD47 in cell proliferation and apoptosis that the drug would radioprotect normal cells and radiosensitize cancer cells. However, using the prostate cancer cell line PC3 in cell proliferation and cytotoxicity assays, I observed that the CD47 knockdown produced the same response in both cell types; the treatment dramatically increased growth and viability. I used flow cytometric analysis, q-PCR, and western blot hybridization to investigate the pathways responsible for the observed radioprotection. A 24-hour incubation period for exosomal biogenesis was necessary for radioprotection in Jurkat T-cells and PC3. With a modified transfection procedure, novel insights into the autophagic degradation of CD47 and the drug's possible relation to the non-homologous end joint repair pathway were shown. Results from this project will lead to new avenues for cancer treatment that target the cell mechanism of radioprotection.

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