

Purpose: This research addresses apoptosis within stem cells and necrosis as two common mechanisms of radiation induced tissue injury. Inhibitors of enzyme GSK3 β ; markedly attenuate radiation induced apoptosis in normal tissues but not in cancer. These drugs prevented radiation induced injury in brain, intestine, bone marrow and skin. Here we develop noninvasive imaging as a means to monitor radioprotection by GSK3 inhibitors.

Methods: Specific inhibitors of GSK3, SB2 and SB4, were administered to mice by IP injection prior to irradiation. Single-treatment Gamma Knife doses of 15-60Gy were given to the 50% isodose volume (33.5mm³) in one mouse brain hemisphere. T2-weighted, microMRI of the brain was performed weekly. Whole abdominal doses of 7-8Gy were used to treat intestine. F18-labeled apoptosis radiotracer was manufactured in the radiochemistry laboratory and was injected by tail vein in mice at 24 hours after irradiation. MicroPET imaging was performed to monitor uptake of the apoptosis detector following irradiation.

Results: Radiation induced apoptosis in the brain and intestine occurred after 24 hours in a dose dependent manner with doses as low as 2Gy. Brain necrosis was compared histologically with imaging following 15-60Gy and was first detected 3-7 weeks after irradiation. GSK3 inhibition prevented radiation induced apoptosis and preserved organ function in irradiated mice. MRI detected brain necrosis in mice treated with Gamma Knife. The apoptosis radiotracer has a short half life which is sufficient because apoptosis is transiently detected at 24 hours after irradiation. Renal excretion of the radiotracer allows imaging of radiation induced apoptosis in intestinal crypts after abdominal irradiation.

Conclusions: Radioprotection of the brain and intestine by GSK3 β ; inhibitors can be monitored by MRI and PET imaging. Radiotracers with a high sensitivity for apoptosis are needed to monitor apoptosis. These imaging modalities are needed for the planned clinical trials of GSK3 inhibitors as radioprotectors.