Ionizing Radiation Targets Endothelium to Induce Normal and Neoplastic Tissue Damage

These studies focus on the role of the microvasculature in tissue damage. Endothelial cells generate 20-fold more of a unique form of acid sphingomyelinase (ASMase), termed Secretory ASMase, than any other cell in the body. Secretory ASMase activation is required for ionizing radiation to kill endothelium (Santana et al., Cell 1996; 86:189-199), as endothelium in lung, gut, and brain are totally resistant to radiation-induced apoptotic death in the absence of ASMase. Furthermore, we have provided evidence that there is a biologic/therapeutic consequence of this phenotypic response, that is, that high single dose radiotherapy (SDRT), an emerging mode of radiotherapy capable of curing radioresistant cancer, requires ceramide-driven endothelial apoptosis for tumor cure [Garcia-Barros et al., Science 2003; 300:1155-1159; Truman et al., PLoS ONE 2010; 5(9)]. This observation has broad implications for cancer treatment, and is actively debated in the field, as it is generally believed that radiation therapy works exclusively by targeting tumor stem cells and that the tumor microenvironment is not an important player in radiation cure. Based on this observation we have generated an adenoviral gene therapy vector to overexpress human ASMase exclusively in neo-vasculature and are observing dramatic radiosensitization of tumor cure in mouse models, even in tumors completely resistant to conventional fractionated radiotherapy. We are at the beginning stages of taking this adenoviral vector to the clinic for treatment of radiation incurable cancer.

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