Comparative analysis of Fe ion-induced mutations in murine tissue and cells

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Space flight exposes astronauts to densely ionizing heavy ions, including Fe ions. This study is designed to assess the impact of the tissue microenvironment on the cytotoxic and mutagenic effects of 1 GeV/amu Fe ions in kidney epithelial cells from one mouse strain irradiated either *in vitro* or *in vivo*. Three to five month old *Aprt* heterozygous mice are used from a C57BL6/DBA2 cross (B6D2F1) or kidney cells are used that were established from these mice. Cells and animals were exposed in the plateau portion of the Bragg peak (159 keV/μm) at the NASA Space Radiation Laboratories (NSRL) at Brookhaven National Laboratory. Approximately equal numbers of male and female animals were used for the *in vivo* studies.

In vitro experiments demonstrated exponential cell killing with a D(0) of 92 cGy. Three *Aprt* mutation experiments have been performed in kidney cells exposed to graded doses of Fe ions *in vitro* (0-2 Gy). Studies to date indicate that Fe ions are mutagenic to kidney epithelial cells irradiated *in vitro*, with a linear induction of mutants as a function of dose. *In vivo* experiments have been completed on two thirds of the animals planned for the study. Kidney cells were retrieved from the animals at two time points: 2-3 months post-irradiation or 8-9 months post-irradiation. Fe ion exposure *in vivo* led to exponential killing of kidney epithelial cells that was still evident 8-9 months post-exposure. *In vivo* irradiation also results in the induction of *Aprt* mutants and these mutants are not lost from the kidney with incubation times *in situ* of up to 9 months post-irradiation.

We are interested in the molecular basis underlying the acquisition of Fe ion-induced *Aprt* mutants. Such mutants can arise through a panoply of mechanisms, ranging from epigenetic silencing to whole chromosome loss. Ongoing molecular analyses of Fe ion-induced *Aprt* mutants collected from cells exposed either *in vivo* or *in vitro* demonstrates a distinct pattern of events that appear driven by the induction of DNA double-strand breaks. As such, they resemble other autosomal mutations we previously characterized that arose in human cells exposed *in vitro* to the same Fe ion beams.

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