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Radiation Leukemogenesis

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Radiation exposure increases the risk of developing leukemia, particularly acute myeloid leukemia (AML). In humans, the average excess relative risk per Sievert is about 4.3 and the latency is about 68 months, which is short when compared to solid tumors. Extrapolating epidemiological data on radiation leukemogenesis to risk assessments for space flight crews presents several challenges, particularly with regard to differences in radiation quality and dose rate effects.

Some inbred strains of mice are susceptible to radiation-induced AML. In these strains, fission spectrum neutrons are more effective than gamma-rays in AML induction with an RBE of about 3, while 60 MeV protons are only about as effective as gamma-rays. With low LET radiation, decreasing the dose rate results in fewer AMLs. In both mice and humans, one AML initiating event appears to be the radiation-induced deletion of a specific chromosomal region: chromosome 2 encompassing the *PU.1* gene in the mouse and chromosomes 5q and/or 7q in the human. In mice, *PU.1*, which is a lineage specific transcription factor expressed during myelopoiesis, behaves like a classic tumor suppressor gene. One copy is lost due to deletion and the remaining allele is frequently mutated. A direct role for in *PU.1* mutation in human AML is controversial, but *PU.1* activity is often decreased in human AML. Identifying the specific gene or genes in the deleted regions of human 5q and 7q that are critical for leukemogenesis is an area of intense investigation.

We have investigated the efficacy of 1 GeV iron particles for the induction of AML and found an RBE of about 1, which is unexpected based on previous results obtained with neutrons. Interestingly, both gamma-ray and iron particle irradiation give rise to bone marrow cells carrying *PU.1* deletions that can be detected 24 hours post-irradiation, but while the proportion of bone marrow cells with *PU.1* deletions increases at 1 month post-irradiation in gamma-ray irradiated mice it decreases in iron particle irradiated mice. By one year post-irradiation, the proportion of cells with *PU.1* deletions returns to high levels in iron particle irradiated mice. One interpretation of the deletion data is that although iron particles are efficient in generating *PU.1* deletions which are an initiating event in leukemogenesis, they are also efficient in cell killing. Thus many of the cells with *PU.1* deletions detected one day after iron particle irradiation have additional damage that will lead to cell death and by one month post-irradiation these cells have been cleared from the bone marrow. Some of the surviving cells with *PU.1* deletions undergo additional mutations that lead to a proliferative advantage reflected by increased numbers of *PU.1* deleted cells at one year post-irradiation.

Another interesting finding is that bone marrow cells with *PU.1* deletions can be detected 24 hours after gamma-ray or iron particle irradiation of an AML resistant strain, C57BL/6, but by one month post-irradiation these cells have been removed from the bone marrow. These results suggest that the persistence of *PU.1* deleted cells in the bone marrow is a requisite for leukemogenesis in the murine model.

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