A systems genetic analysis of susceptibility to development of tumors induced by high LET radiation

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p53 promotes tumor suppression by activating a myriad of pathways, such as apoptosis and cell cycle arrest, which enable the maintenance of genomic integrity. Germline deletion of a small N-terminal proline-rich region of p53 in an *in vivo* mouse model (p53 ΔP) causes no spontaneous tumors. However, upon exposure of the p53 ΔP mouse to both low (Yu *et al*., in preparation) and high LET (linear energy transfer) radiation, a wide range of solid tissue tumors develops, including those of the liver, lung and kidney. This range is in stark contrast to the tumor spectrums in the p53 *null* mouse post-radiation, the majority of which are lymphomas and sarcomas. Therefore, the p53 ΔP mouse represents an exquisitely radiation-sensitive model to study radiation-induced tumors similar to those seen in the human population.

We have initiated long-term tumorigenesis assays using p53 ΔP mice, aged between 6-10 weeks, upon both mixed background (129/Sv/C57BL/6) and FVB background. 110 p53 ΔP mice on a mixed 129/Sv/C57BL/6 background have been irradiated with either 29 cGy, 81 cGy, or 1 Gy 600 MeV Fe particles or 1 Gy gamma radiation. In addition, wild-type controls of 129/Sv or C57BL/6 mice were irradiated. In the FVB background we have irradiated 250 p53 ΔP, WT and p53 heterozygote mice with 50 cGy of either 600 MeV Fe particles or gamma radiation. Control mice on 129/SV, C57BL/6 and FVB background have not yet succumbed to any tumor development, whilst on the p53 ΔP and p53 heterozygote mice many tumors have been observed on radiosensitive tissues including the skin, liver, lung, breast, thymus and spleen. Tumors are being harvested for both histology and gene expression analysis, and studies are still ongoing. Preliminary analysis of the data indicate that both 600 MeV Fe particles and gamma radiation induce solid tumors in p53 deficient mice, yet also suggest that the tumor spectrum may differ depending on radiation quality. Currently, there are no studies describing the impact of high LET radiation upon the FVB genetic background, therefore these long-term tumorigenesis studies will provide valuable information as to the impact of genetic background upon heavy-ion radiation-induced carcinogenesis.

Furthermore, in order to gain a greater insight into the mechanism by which both low and high LET initiate tumorigenesis we will use a systems genetics approach. In this manner we will generate an intricate network view, which will enable the identification of genes and pathways associated with susceptibility to radiation-induced tumors. Ultimately, this data will assist in the identification of potential genetic susceptibilities for future assessment in human populations.