Radiation Response Genes in the Worm Caenorhabditis elegans

For [illegible] nserved gene functions and their geneti [illegible] interactions after ionizing radiation using the nematode *C. elegans*. In many instances where mammalian systems are too complicated to obtain clear information concerning signaling pathways, *C. elegans* has been instructive. Mammalian systems often have multiple isoforms of an enzyme; whereas *C. elegans* may possess a single form. Further, mammalian tissue diversity has many times resulted in the utilization of signaling proteins in a combinatorial manner. The simplicity of the *C. elegans* system coupled with the capacity to readily incorporate more than 1 mutated allele in a single animal make this model ideal for asking questions regarding the molecular ordering of signaling cascades.

Our laboratory has focused on several gene pathways involved in the sensing of radiation damage and the signaling of apoptotic and post-mitotic (reproductive) death in germ line. In our previous studies we identified *C. elegans* ABL-1, the homolog for human c-Abl and demonstrate that ABL-1 plays an anti-apoptotic role in the C. elegans germ line by acting as a negative regulator of the p53 homolog CEP-1 (Nature Genetics, 2004). Subsequently we characterized 24 genetic mutants of the C. elegans sphingolipid metabolic pathway. We initially defined CEP-1/p53-mediated EGL-1 up-regulation and ceramide synthase-mediated ceramide generation on parallel pathways that integrate at mitochondrial membranes to co-regulate the stress-induced apoptotic checkpoint (Science, 2008). We are in the process of screening genes involved in ionizing radiation-induced DNA repair using a *C. elegans* germ line tumor model. Data to date indicate specific relevance of the homologous recombination DNA repair apparatus in potential therapy for Notch driven tumor stem cell lethality.

Deng, X, Hofmann, ER, Villanueva, A, Hobert, O, Capodieci, P, Veach, DR, Yin, X, Campodonico, L, Glekas, A, Cordon-Cardo, C, Clarkson, B, Bornmann WG, Fuks, Z, Hengartner, MO and Kolesnick, R. Caenorhabditis elegans ABL-1 antagonizes p53-mediated germline apoptosis after ionizing radiation. Nature Genetics 2004; 36:906-12.

Deng X, Yin X, Allen R, Lu DD, Haimovitz-Friedman A, Fuks Z, Shaham S, Kolesnick R. Ceramide biogenesis is required for radiation-induced apoptosis in the germ line of C. elegans. Science. 2008 Oct 3;322(5898):110-5.