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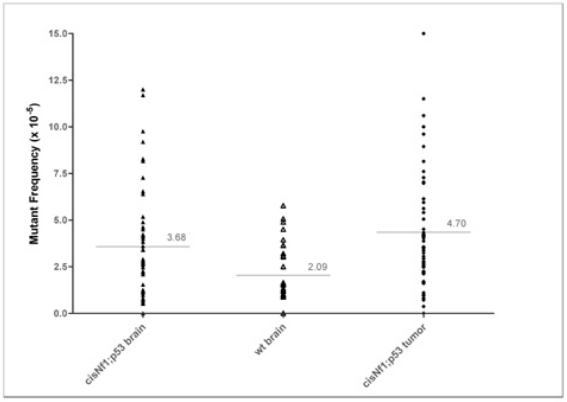
Neurofibromatosis Type 1 and Genomic Instability

Neurofibromatosis Type 1 (NF1) is a common genetic cancer syndrome that primarily affects derivatives of the neural crest, including Schwann cells and melanocytes; other tissues, such as bone and the CNS, are also involved in some patients. The expressivity, progression, and prognosis for NF1 can be highly variable, even among family members with the same germline mutation in the NF1 gene. Currently, my laboratory uses a mouse model for peripheral nerve sheath tumors (PNST), which I generated as a postdoctoral fellow in Dr. Luis Parada's laboratory, to examine the contributions of genomic instability to NF1 disease progression.

Two ongoing collaborations with other C&SB faculty focus on spontaneous mutagenesis in PNST, and on DNA repair mechanisms in PNST cell lines. With Dr. Chris Walter, we have characterized the spontaneous mutant frequency in tumors and normal tissues in our PNST mouse model (cisNf1+/-;p53+/-). With Drs. Olivia Perreira-Smith and Kaoru Tominaga, we are examining contributions of the chromodomain protein-encoding gene Mrg15 in tumorigenesis for our mouse PNST model. Recently, we've used the comet assay to show that Mrg15 deficiency slows the DNA repair process in PNST cell lines exposed to ionizing radiation.



Spontaneous mutant frequencies, measured in tumors and brains isolated from cisNf1;p53 mice, using the lacI transgene.

We also compared DNA damage sensitivity and DNA repair capacity in Schwann cells (the cell-of-origin for PNST) isolated from young and old Nf1+/- and Nf1+/+ mice, and found that in both genotypes, the ability to repair DNA double strand breaks declines with age.

Nf1 Gene Expression and Apoptosis during Embryonic Development

Using a targeted null mutation in the Nf1 gene, generated over 10 years ago by Dr. Cami Brannan, I've been able to demonstrate that the neurofibromin protein plays an important role in modulating the survival response to neurotrophins in embryonic neurons. A collaboration with Dr. Patricia Dahia and Y. Qin, focusing on the Egln3 gene, continues this research interest in the context of the sympathoadrenal lineage. We isolate sympathetic and sensory neuronal precursors from mouse embryos harboring Nf1 and p53 mutations, and compare responses to withdrawal of neurotrophin survival factors, such as NGF. This classic experimental paradigm in developmental neurobiology can be applied to characterize mechanisms of pheochromocytoma tumorigenesis, and to confirm susceptibility mutations.