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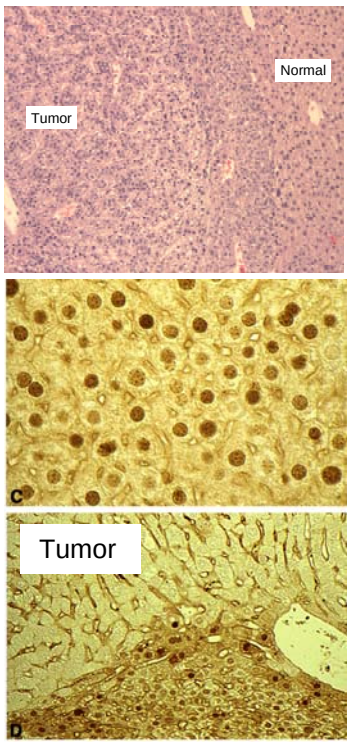
Genetic integrity is necessary for many important biological processes including DNA replication, transcription, and successful reproduction. Significant defects in genetic integrity can lead to reproductive failure, mutagenesis, cancer, and potentially aging and age-related diseases such as Parkinson's disease and Alzheimer's disease. My research interests are focused on understanding the extent to which DNA repair mechanisms function to maintain genetic integrity and how deficiencies in DNA repair impact biological processes such as mutagenesis, carcinogenesis, reproduction and aging.

One project involves transgenic mice developed in our laboratory that display increased resistance to spontaneous hepatocellular carcinoma. The transgenic mice overexpress a DNA repair protein, human O6-methylguanine-DNA methyltransferase (MGMT), in brain and liver. In addition, the frequency of GC to AT transition mutations is reduced by 50% in the TF/MGMT mice at 15 months of age. Unrepaired O6-methylguanine leads to GC to AT transition mutations if not repaired. These data indicated elevated in vivo MGMT activity. Loss of MGMT expression was observed in tumors and led us to hypothesize that loss of MGMT could contribute to the etiology of spontaneous hepatocellular carcinoma.

Hepatocellular Carcinoma



Preliminary studies with the mouse model have revealed that monofunctional alkylating agents may be effective therapeutic agents agents. We are currently studying the efficacy of a clinically relevant alkylating agent using the mouse model. If successful, we will move into translational studies.

Hepatocellular carcinoma. Hepatocellular carcinoma detected in mouse liver (top panel). Immunohistochemical staining reveals brown nuclei in cells expressing MGMT (middle panel). Tumor tissue is devoid of MGMT expression (bottom panel).