Cancer Molecular Pathology

Research Synopsis

1. Overview

My research laboratory uses a multidisciplinary approach involving genomics and bioinformatics along with cell culture and animal models to study recurrent chromosomal alterations, such as translocations and amplification, in cancer. Our major current focus is rhabdomyosarcoma (RMS), a family of myogenic soft tissue cancers usually occurring in children, in which we are investigating the genetic basis, biological consequences, and therapeutic implications of chromosomal alterations. In addition, my laboratory works closely with pediatric oncologists and other clinical specialists to investigate the utility of these recurrent chromosomal alterations as biomarkers for diagnosis and management.

2. Molecular genetics of alveolar rhabdomyosarcoma

During the last two decades, my research laboratory has conducted studies to unravel the fundamental events responsible for an aggressive RMS subtype known as alveolar RMS. After cytogenetic studies of this cancer identified translocations between chromosome 13 and either chromosome 2 or chromosome 1, my laboratory identified that these translocations break the PAX3 gene on chromosome 2 or the PAX7 gene on chromosome 1, and join part of these genes with part of the FOXO1 gene on chromosome 13. This process results in the formation of PAX3-FOXO1 and PAX7-FOXO1 fusion genes, which encode aberrant transcriptional regulators. My laboratory’s recent studies are investigating how these fusion proteins function in the cancer cells, and are exploring how to manipulate fusion protein expression and function with the ultimate goal of developing novel strategies for therapeutically targeting these fusion proteins.

To complement these studies of fusion proteins, my laboratory is also investigating additional changes that occur in alveolar RMS and cooperate with the fusion protein during RMS tumorigenesis. To search for such events, we performed genome-wide screens of DNA copy number changes and small DNA changes. These studies revealed that, though there are few if any recurrent small DNA changes in ARMS, there are frequent changes in which chromosome regions increase in copy number by genomic amplification and result in high expression of genes within these amplified regions. Current studies are identifying the proteins encoded by these amplified regions, the specific function of these proteins in alveolar RMS, and strategies to manipulate expression or function of these proteins. In addition, my research laboratory is also performing additional genome-wide screens to investigate changes that occur at the level of DNA methylation, a type of DNA modification that influences gene expression by altering how the DNA packages with nuclear proteins. These studies have identified numerous characteristic DNA methylation changes in alveolar RMS and are analyzing how these changes alter gene expression and function in this cancer.

3. Clinical translation in pediatric sarcomas

To investigate the clinical utility of gene fusions, amplification and other DNA changes, I also established a translational research program exploring the role of these molecular markers in the diagnosis, prognosis, and management of pediatric sarcomas. These studies are addressing both molecular approaches for detection of these changes in tumors and the correlation of these molecular findings with clinical characteristics, including patient outcome. Many of these studies are performed as part of the Soft Tissue Sarcoma Committee of the Children’s Oncology Group, an international organization devoted to translational studies of pediatric cancer. The findings of these clinical research studies are now being incorporated into the next set of clinical trials conducted by the Soft Tissue Sarcoma Committee.