"Investigation of the ATRX-Daxx Chromatin-remodeling Complex in Pancreatic Neuroendocrine Tumors"

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Abstract: Pancreatic neuroendocrine tumors (PanNETs) are a poorly understood and clinically challenging type of cancer. A recent report indicates that the genes encoding subunits of the ATRX-Daxx chromatin-remodeling complex are frequently mutated in a sporadic, non-functional PanNETs. The ATRX-Daxx complex is proposed to regulate gene expression pathways and maintain genome integrity primarily through specialized chromatin assembly pathways that involve the histone H3 variant, H3.3. In this proposal, we will use a variety of cell-based, molecular and biochemical assays to gain an enhanced understanding of how the ATRX-Daxx-H3.3 complex helps maintain pancreatic neuroendocrine cell identity. We will expand the search for genetic lesions in the ATRX-Daxx pathway to all types of pancreatic neuroendocrine tumors. Additionally, we seek to determine how loss of the ATRX-Daxx pathway leads to changes in gene expression pathways and epigenomic signatures in panNET versus normal samples. Using a combination of structural and biochemical assays we will gain mechanistic insight into how the ATRX-Daxx complex is targeted to specific genomic loci, and how this complex carries out chromatin assembly, paying attention to telomeric loci based upon past work. We also propose to directly test if the ATRX-Daxx complex functions as a tumor suppressor through the construction of a mouse model. Specifically, we will determine whether genetic deficiency of Daxx in subtypes of pancreatic neuroendocrine cells is sufficient to induce tumorigenesis. The characterization of the ATRX-Daxx complex deposition pathway will have a significant impact in cancer research and will fit well within the mission statement of the SCC. The recent identification of both ATRX and Daxx as potential tumor suppressor genes suggests that this H3.3-deposition pathway plays a critical role in maintaining cellular identity and genomic integrity in pancreatic neuroendocrine cells. To accomplish this long-term goal, our collaborative team will tap into the proven expertise of a world-renown group of chromatin biologists (Allis - Rockefeller), structural biologists (Patel - MSKCC) and cancer physician scientists (Tang and Hsieh - MSKCC).