Genetics Day Poster Submission

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Title: SPLICING REGULATION AS A MOLECULAR DRIVER OF BASAL PANCREATIC CANCER

Abstract: Pancreatic ductal adenocarcinoma (PDAC) is the 4th leading cause of cancer deaths in the US, and among the most fatal, with a 5-year survival rate of 10%. Through molecular characterization, two primary PDAC subtypes have been identified: a classical subtype, which is better differentiated and have high expression of adhesion-associated and epithelial genes; and a basal-like subtype, with a poorer clinical outcome, therapeutic resistance and loss of differentiation. Recent research has shown that basal-like PDAC can arise when the often mutated component of the SWI/SNF chromatin remodeling complex Arid1a is lost. Our first observations suggest the same basal-like phenotype when the long non-coding RNA Neat1, which is necessary for the assembly of nuclear paraspeckles, is lacking, which raises a number of potential pathways that could be involved in this process. Interestingly, these genes appear to be involved in the same molecular mechanisms that drive basal-like PDAC subtypes. Specifically, we have discovered that both Neat1-deficient and Arid1a-deficient pancreatic cells fail to form nuclear paraspeckles, i.e. structures implicated in the regulation/attenuation of RNA splicing. RNA-seq data analysis also showed an increase of expression of splicing-related genes in both paraspeckle-deficient cell types. Based on preliminary data, it appears that suppression of PRMT5, an arginine methyltransferase protein important for splicing, causes basal-like cells to exhibit traits indicative of a classical subtype. When splicing is hindered by drugs that block the PRMT family of proteins, the same phenotypical change is seen. Another significant observation is the decrease in BrdU incorporation and colony formation after PRMT inhibition in basal-like PDAC cells, which indicates less cell proliferation and clonogenicity. Furthermore, it was demonstrated that cell migration, a characteristic enhanced in basal-like subtypes, is diminished in a basal-like cell wound healing assay in which splicing was pharmacologically repressed. Overall, these findings support the hypothesis that splicing catalysis upregulation caused by paraspeckle loss is important for the basal-like PDAC subtype. It also support that RNA splicing could be a potential target intervention in patients with the most aggressive and recalcitrant PDAC subtypes.