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Title: INVESTIGATING THE ROLE OF NEAT1 IN RESTRICTING THE FORMATION OF PANCREATIC CANCER

Abstract

Pancreatic ductal adenocarcinoma (PDAC) is the 4th leading cause of cancer deaths in the US, and is expected to become the second leading cause by 2030. Defining the mechanisms behind PDAC initiation is critical for the development of new diagnostic tools and therapeutic targets. We have discovered that loss of the p53-controlled long noncoding RNA (lncRNA) Neat1 promotes loss of cell identity and enhances the formation of preneoplastic lesions in mouse models of PDAC. Neat1 loss leads to significant changes on chromatin organization and on the distribution of the SWItch/Sucrose Nonfermentable (SWI/SNF) chromatin remodeling complex at the chromatin, suggesting that Neat1 maintains cell identity in the pancreas by impacting SWI/SNF function. SWI/SNF contains an initial core complex that additional subunits can interact with to form one of three variants: canonical BAF (cBAF), polybromo-associated BAF (pBAF) and non-canonical BAF (ncBAF). While cBAF controls enhancers preferentially, pBAF and ncBAF are typically found to bind promoter regions. Interestingly, Neat1 deficient mice closely mirror mice deficient for the SWI/SNF component Arid1a, which is a cBAF-specific subunit. Additionally, preliminary data suggests that Neat1 loss leads to decreased SWI/SNF binding at enhancer regions, supporting the idea that Neat1 loss is impacting cBAF. Neat1-SWI/SNF physical interaction has been previously described in the literature, and could support a mechanistic basis for Neat1 impact over SWI/SNF. However, preliminary data show that Neat1 and SWI/SNF do not occupy the same regions of chromatin, suggesting that a physical Neat1-SWI/SNF interaction might occur before SWI/SNF is fully assembled and ready to control DNA accessibility. With this data taken together, I hypothesize that Neat1 interacts with SWI/SNF in a chromatin-free manner, and by doing so it supports cBAF function, restricting the formation of precancerous pancreas lesions. This research aims to 1) Define the impact of Neat1 loss on cBAF function, and 2) Define the nature of the interaction between Neat1 and SWI/SNF in the pancreas, as well as its impact on SWI/SNF activity. The work from this project will elucidate the role of Neat1 in restricting the formation of preneoplastic pancreas lesions, and how the SWI/SNF machinery is impacted by Neat1.