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Parathyroids

Pancreas

QP

Figure 1. Tissue-specific tumorigenesis

MEN1 Syndrome. www.niddk.nih.gov

Introduction

While a germline heterozygous mutation in the Multiple Endocrine Neoplasia type 1 (MEN1) gene predisposes tumor formation in the endocrine pancreas, parathyroid glands and anterior pituitary this tissue-specific (**Fig.1**), tumorigenesis is not dependent on MEN1 mutations alone. In fact, a homozygous deletion of *Men1* in mouse pancreatic exocrine tissue does not result in tumor formation, suggesting an endocrine tissue-specific mechanism.



hypermethylation in MEN1 tumors [2].

Loss of menin activates a menininteracting protein retinoblastomabinding-protein 5 (RBBP5). Since RBBP5 transcriptionally regulates DNA methyltransferase (DNMT1), this causes global DNA hypermethylation and subsequent tumorigenesis in MEN1-target endocrine tissues (Fig.2,3).

Thyroid -



tumors compared to normal human parathyroid, sporadic parathyroid adenomas and parathyroid carcinomas [2].

Hypothesis

We hypothesize that while RBBP5 is ubiquitously expressed, if exclusively binds to the DNMT1 promoter in MEN1-target-tissues through its recruitment by tissue-specific factors.



Tissue-Specific Tumorigenesis in Multiple Endocrine Neoplasia Type I

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Conclusions

Rbbp5 binds the *Dnmt1* promoter in MEN1-target-tissues and Nkx2.2 and Pax5 are candidates for Rbbp5 recruitment to the Dnmt1 promoter that must be tested further to determine their role in the observed tissue specificity of MEN1-related tumorigenesis.

Future Studies

Validate the role of Rbbp5, Nkx2.2 and Pax5 in MEN1 tumorigenesis by in vivo knock-out of factors using CRISPR genome editing in *Men1* ko mice. By knocking these factors out in a Men1 ko mouse, we will determine their necessity in MEN1 tumorigenesis.

•Our overall goal is to understand the tissue-specific mechanism of MEN1 pathogenesis for development of future therapeutic interventions.

gene x



Mouse with *Men1* ko in whole pancreas **TVA expression under RIP promoter (beta** cells), with whole pancreas Cas9 expression

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