Understanding CDKN1C and its Implications in Endocrine Disorders

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Introduction

CDKN1C is an inhibitor of the G1 phase of the cell cycle and is thought to be involved in regulating terminal differentiation in the pancreas and adrenal glands. Many newborns with CDKN1C mutations have Beckwidth-weidemann syndrome, characterized by large stature and hyperinsulinemia, but a certain subset have the opposite phenotype, called IMAGe syndrome, characterized by short stature and adrenal hypoplasia congenita. One specific mutation we investigate also results in early adult onset diabetes.

Hypothesis

In this project we test two hypotheses. The first is that IMAGe-like syndrome leads to early adult onset diabetes due to hypoinsulinemia secondary to decreased pancreatic beta cell proliferation. The second is that the increased stability of CDKN1C is responsible for the IMAGe and IMAGe-like syndromes' phenotypes.

Methods

We used a knock-in mouse model for the homologous mutation to IMAGe-like syndrome in humans to investigate the effects of CDKN1C on various organs. To investigate CDKN1C stability, we designed a cell transfection & treatment experiment to explain previous inconsistencies found in the literature.

Results

Knock-in mice demonstrated difficulty surviving past 4 weeks and variable adrenal abnormalities but did not demonstrate growth restriction or islet pathology. The stability experiment demonstrated evidence against the ubiquitin-proteasome degradation pathway for CDKN1C and suggested that its life cycle is more complex.

Conclusions

CDKN1C appears to have a wide array of cellular activities, as evidenced by its multi-organ prevalence and variability among species. It also appears to have a more complicated life cycle than simple ubiquitination and proteasome degradation. Understanding there interactions better could lead to novel therapies for difficult to treat cases of diabetes and growth disorders.

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