Cell-Cycle Regulators p27 and Cyclin D1 in Pten Null Adult β-Cell Islets

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In this study, we examine the roles of p27 and cyclin-D1 and their effect on beta cell cycle progression. We propose that after deleting PTEN in the beta-cell, there will be a downstream enhancement of cyclin-D1 and inhibition of p27, disabling cell-cycling inhibitors and stimulating an increase in beta-cell replicating power.

METHODS

Previously, in the lab, mice were crossed in order to obtain F2 generation experimental male mice. The genotype of the mice are: PtenloxPlox/+; Rosa26lacZ/lacZ; RlckCre+/+; mice in order to delete PTEN from the beta-cell. The experimental mice were CreER+ mice treated with Tamoxifen. The control mice were CreER− mice treated with corn oil and CreER− mice treated with Tamoxifen or corn oil. CreER− mice target the PTEN gene for deletion when Tamoxifen is present, while CreER+ mice do not and CreER+ mice without Tamoxifen do not. The experimental mice have targeted deletion of PTEN in their beta-cells and were autopsied and dissected to obtain slides of pancreatic tissue. The PTEN gene remains intact in the control mice. Prior to my experiments, the mice had also been genotyped from tail DNA using standard genomic PCR techniques. All of these experiments were conducted according to the Institutional Animal Care and Use Committee of the University of Southern California research guidelines.

RESULTS

In this figure, genomic PCR results show the control (Tam) and PTEN null (Tam +) DNA isolated from mouse islets.

- Tamoxifen + Tamoxifen
- Insulin + p27 + DAPI
- Insulin + Cyclin D1 + DAPI

DISCUSSION

Our study shows that beta-cells are regulated by different factors that cause it to reproduce in a very organized and specific way. Beta-cells are naturally equipped with these inhibitors and promoters to drive a balanced system for controlling cell-cycle progression. Because of its low level of replication in adult life, working on the manipulation of these factors and proteins in order to encourage beta-cell replication in a way that protects the pancreas from a tumorigenic state would be a potential next step for subsequent research. If the beta-cell can be induced into safe replication in adulthood, its cells may potentially be better prepared for any exhaustion, metabolic disruption, or insulin-resistance that may occur, which points towards potential therapeutic treatments for type 2 diabetes.

CLINICAL SIGNIFICANCE

Several reports suggest cyclin D1 enhances cell growth and survival. The increase in cyclin D1 levels as a result of deleting PTEN indicate that cyclin D1 may be a downstream target of the PI3K/AKT signaling pathway.

- During the transition between the G1 and S phase of the cell cycle, p27 (unphosphorylated) enters G1 arrest. D1 cyclin phosphorylates p27 to release cells from G1 arrest and progress them through the cell-cycle.
- Studies suggest that p27 is involved in the inhibition of the cell-cycle. The decrease in p27 levels as a result of deleting PTEN suggests that p27 may also be a downstream target of the PI3K/AKT signaling pathway.
- Cyclin D1 must form a complex with cyclin-dependent kinase-4 or -6 in order to phosphorylate p27. The role of p27 has been understood to bind to this cyclin D1/cdk complex and prevent them from phosphorylating p27.
- When PTEN is deleted, the PI3K/AKT pathway up-regulates cyclin D1 and inhibits the cyclin D1 regulator p27. Thus, the cells move unchecked into the S phase of the cell cycle. This promotes cell growth, increasing adult beta-cell replication.