MODELING CARDIAC COMPLICATIONS OF DIABETES IN MICE

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Approximately 6.3% or 18.2 million people in the United States suffer from diabetes. Cardiovascular disease accounts for 80% of diabetes-related deaths. Diabetes is associated with profound changes in cardiac metabolism that reduces ATP production and increases the risk of heart failure.

Mice with a cardiomyocyte-selective insulin receptor knockout (CIRKO) using cre/loxP recombination was generated to study the role of insulin signaling on postnatal cardiac development and cardiac metabolism (2). Cre is an enzyme that causes recombination (deletion) of DNA sequences that are flanked by 34 base-pair loxP sites. CIRKO mice were generated by crossing mice that were homozygous for an insulin receptor allele flanked by loxP sites (IR lox/lox) with IR lox/lox transgenic mice containing cardiomyocyte restricted expression of cre recombinase (by driving cre expression with the alphasatrin heavy chain promoter). CIRKO mice have the genotype Cre::IR lox/lox. These mice displayed the absence of insulin receptors from their cardiomyocytes since birth because cre mediated recombination of the insulin receptor resulted in a frame shift mutation that introduced a premature stop codon into the insulin receptor gene. CIRKO mice phenotypically exhibited a reduction of cardiomyocyte size by 20-30% with about 36% decrease in cardiac output compared to controls.

A tamoxifen-inducible cre recombinase protein fused to two mutant estrogen-receptor ligand-binding domains (MerCreMer) under the control of the alphasatrin heavy chain promoter were crossed with IR lox/lox mice to generate mice with temporally controllable deletion of insulin receptors in cardiomyocytes.

The mutant estrogen receptor (Mer) is insensitive to estrogen but is activated by the antagonist of estrogen (tamoxifen) (3). In the absence of tamoxifen, cardiomyocyte insulin receptor expression is normal in MerCreMer IR lox/lox mice. When tamoxifen is administered to these mice, the MerCreMer fusion protein is activated and migrates to the nucleus where it causes recombination of the loxP containing insulin receptor alleles.

This subsequently leads to loss of insulin receptors from cardiomyocytes. Thus MerCreMer transgenic mice allow for temporal regulation of gene expression in vivo.

In conclusion, both CIRKO and MerCreMer mice allow for the examination of insulin signaling on postnatal cardiac metabolism, physiology and cardiac development. CIRKO mice are born without insulin receptors while MerCreMer is an inducible form of CIRKO that can inactivate insulin receptors in adult hearts following activation of the transgene by tamoxifen. They both represent valuable tools with which to model the role of altered myocardial insulin signaling in the cardiac complications of diabetes.

Reference:

