Abstract:

Obesity and type 2 diabetes are major health problems in the world. There are several risk factors for type 2 diabetes such as age, obesity, pregnancy, stress, and genetics. Approximately 90% of diabetic people with type 2 are obese or overweight. This thesis aims to develop and improve the metabolism by regulating obesity by focusing on a gene called *RCAN1*. Regulator of calcineurin 1 (RCAN1) is a gene located on chromosome 21 and primarily expressed in adipose tissue, liver, brain, heart, skeletal muscle, and pancreas. It has a well-known role as an endogenous inhibitor of the phosphatase, calcineurin, which is important for the transcription factors in the cells. RCAN1 has two main isoforms named RCAN1.1 and RCAN1.4. These isoforms result from alternate transcripts with unique promoters and first exons. RCAN1 plays essential roles in metabolism, such as regulating obesity. Unpublished data from our lab shows that RCAN1 knock out mice are protected from obesity when placed on a high fat diet, indicating that this gene controls obesity by reducing fat mass. Furthermore, mice lacking RCAN1 show enhanced activation of an adaptive thermogenesis program in white adipose tissue under high fat diet conditions. In other words, RCAN1 plays important roles in whole body thermogenesis, which increase weight loss, in a process called adipocyte 'browning'. A practical way to reduce obesity may therefore be through the use of drugs that can inhibit RCAN1. IRCA drugs (IRCA1, IRCA2, IRCA3, IRCA4, and IRCA5) have been identified as RCAN1 inhibitors.

In this project, we focused on four different aims in relation to RCAN1 and its role in obesity. First, we examined *Rcan1* expression in relation to age in white adipose tissue to see whether the expression increases with age. Second, we examined the expression of *Rcan1* in white adipose tissue in relation to diet in mice after a high fat diet compared to a normal fat diet. Third, we measured the expression of genes associated with thermogenesis in white adipose tissue in the apresence or absence of Rcan1 in mice. Finally, we tested whether five RCAN1 inhibitors can affect fat storage in an adipocyte cell line RCAN1-associated metabolic phenotypes *in vitro*. This aim was approached by treating 3T3-L1 cell lines with IRCA Drugs to test the effect of them on differentiation and after differentiation. This study found that *Rcan1* expression does not change across different ages in white adipose tissue. In addition, the data shows that *Rcan1* gene expression seems to increases in white adipose tissue after a high fat diet compared to the low fat diet. The expression of thermogenesis genes seems to decrease in wild type white adipose tissue compared to Rcan1 knockout tissue. Furthermore, we provide a novel

method to regulate obesity by using IRCA drugs that inhibit the function of RCAN1 to reduce fat mas in *vitro*. All of these drugs found to have an effect of reducing fat mass on the cell line that we used by different percentage.