AIMS & OBJECTIVES

CHAPTER 2

Chapter 2. Aims and Objectives

Islet loss and dysfunctionality are important hallmarks of Type 1 Diabetes Mellitus. Our lab has very well documented that *Enicostemma littorale (EL)*, a medicinal plant, is a potent hypoglycemic agent and facilitate islet neogenesis from Pancreatic Stem/Progenitor Cells. Extensive research has also been done on islet biology and fate of pancreatic regeneration and development of endocrine pancreatic islet cells from adult stem/ precursors using swertisin, a C-glucosyl flavone as a lead islet differentiating agent from *EL*. We also found that swertisin exhibited glucose lowering activity in STZ induced diabetic mice. However molecular mechanism of this molecule has not been studied extensively. Hence one of the major focuses of this thesis is to identify molecular targets using *in silico* tools and elucidating its mechanism by further *in vitro* and *in vivo* experiments.

Type 2 Diabetes Mellitus is characterized majorly by insulin resistance. Insulin resistance is caused by unresponsiveness of insulin action. Long term insulin resistance is known to cause various diabetic complications in multiple organs. Skeletal muscle and adipose tissue, insulin sensitive tissues, have been identified as secretory organs. A different panel of myokines is secreted by normally sensitive or insulin-resistant myotubes that impact in a beneficial or detrimental way, respectively, on β -cell function, proliferation, and survival. Secretome of Adipose derived stem cells from adipose tissue secretes large array of factors in the extracellular milieu that exhibit regulatory effects on other tissue including pancreatic islets. The crosstalk of various insulin resistant organs has direct impact on further pathogenesis and severity of the disease.

These generated some key questions which were aimed to be addressed in the current thesis.

- Which are the molecular targets of swertisin in case of its glucose lowering activity? How dynamically swertisin targets its glucose lowering targets (Sodium Glucose Cotransporters (SGLT)? What could be the correlation between mode of action of swertisin and glucose homeostasis by SGLT2?
- Does the secretome exerts trophic effects on islet differentiation? What role these altered secretome plays in islet differentiation? Is there any impact of metabolically compromised muscle and ADSC secretome on differentiation of islet like clusters from pancreatic progenitors?

Thus, we have aimed here to investigate the effect of altered secretome of Adipose derived stem cell and skeletal muscle on islet differentiation along with molecular targets of Swertisin for its glucose lowering activity.

These are the specific objectives of the thesis as follows:

SPECIFIC OBJECTIVES:

Objective-1: Identification of molecular targets of swertisin in glucose homeostasis, islet differentiation & functionality

This objective is further divided as follows

a) *In silico* identification of molecular targets of swertisin
b) *In vitro* identification of molecular targets of swertisin
c) *In vivo* identification of molecular targets of swertisin

Objective-2: Effect of secretome of skeletal Muscle on islet differentiation & functionality

This objective explores the functional, morphological, phenotypic characterization of ILCCs from PREPs under insulin resistant myotube secretome along with islet cell survival and integrity.

Objective-3: Effect of secretome of Adipose derived Stem cells on islet differentiation & functionality

This objective explores the functional, morphological, phenotypic characterization of ILCCs from PREPs under secretome of Adipose derived Stem cells from control and obese along with islet cell survival and integrity.