AIMS AND OBJECTIVES

CHAPTER 2

Aims and Objectives

PARP-1 is a ubiquitous nuclear protein classically known for its DNA repair and cell death mechanisms. However, the perception among the PARP community has shifted to its more profound role in chromatin modulation and controlling expression of transcription factors. In case of diabetes, the regulatory aspect of PARP-1 was brought to light by Okamoto's groups in the early 1990's where they reported that PARP-1 regulates Reg gene expression and induce pancreatic regeneration in 90% pancreatectomised rat model and restored its endocrine function. Ever since then there have been a huge grey area to the possible extrapolations to this report.

The key questions that we raised in this study were

1. Is PARP-1 essential for islet differentiation?
2. Does PARP-1 regulate islet differentiation from pancreatic stem/progenitors?
3. Does PARP-1 play any role in modulating the signaling with respect to islet differentiation?
4. Whether PARP-1 regulates other transcription factors, essential for islet differentiation and beta cell functionality?

Another important aspect of this study was to prove existence, origin and characteristics of pancreatic progenitors, which have been a debatable topic with incongruous point of views, among researchers in the islet biology community. Hence, in this study we have attempted to define pancreatic progenitors for their unique characteristics and islet differentiating potential. Further, the treatment for diabetes mellitus, even with modern medicine is limited to managing the condition with only hope for a cure or an insulin independent life. Pancreatic progenitors have an inherent capacity to form functional islets. Hence, if these cells can be successfully triggered by using certain natural bioactives, we can ameliorate diabetic condition significantly and thus provide an incredible therapeutic intervention. Hence, we have used Swertisin, a potent bioactive with islet differentiating potential whose mechanism has already been reported by our lab in both *in vitro* and *in vivo* models.

Thus, Understanding the mechanistic action of PARP-1 in the paradigm of islet differentiation along with potent bioactives will provide better therapeutics in terms of increasing the islet mass from various stem/progenitor sources for islet replacement therapy for diabetic patients.

Objectives

1. **Establishment of Mice Pancreatic Stem/Progenitors cells for PARP-1+/+ and PARP-1 knockdown (KD) cells.**
2. **Transcriptome analysis of Islet neogenic pathway genes during islet differentiation from PARP-1$^{+/+}$ and PARP-1 KD Stem/Progenitors cells.**
3. **Transcription control of PARP-1 in Islet Neogenesis.**
4. ***In vivo* assessment of role of PARP-1 in pancreatic regeneration in mice.**

The above mentioned objectives are divided into three major chapters of this Ph.D. thesis.

Chapter 3 comprises isolation, characterization and islet differentiation of pancreatic resident progenitors (Objective 1).

Chapter 4 comprises of

A. Establishment of PARP-1 knockdown in pancreatic resident progenitors (Objective 1).
B. Role of PARP-1 in islet differentiation by performing the transcriptome analysis of islet neogenic pathway from PARP-1 knockdown pancreatic resident progenitors, exploring its role in the signal transduction and in transcription control of key genes involved in islet differentiation (Objective 2 & 3).

Chapter 5 comprises of *In vivo* assessment of role of PARP-1 in pancreatic regeneration in mice. (Objective 4)