# 2021 Fall
# LIFE SCIENCES SEMINAR

## "The endoplasmic reticulum stress and its role in the development of obesity and type 2 diabetes"

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- **Date: 4:30PM, September 24(Friday), 2021**
- **Webex ID: 158 406 0140 / PW: 1234**
- **Inquiry: Prof. Sekyu Choi(279-2359)**
- **Abstract:**

The obesity becomes serious health issue by creating significant risks for a variety of diseases including type 2 diabetes, cardiovascular diseases, cancers and recent COVID-19. The endoplasmic reticulum (ER) is the central organelle for protein biosynthesis, folding, and traffic. Perturbations in ER homeostasis (ER stress) and associated signaling cascades (the unfolded protein response, UPR) have been implicated in a variety of metabolic disorders, such as obesity and type 2 diabetes. During the progression of type 2 diabetes, pancreatic β-cell, a major organ to produce insulin to control glucose homeostasis, undergoes functional impairment and ultimate cell loss, critical events of type 2 diabetes. ER stress, in particular PERK-ATF4 pathway of the UPR, has been documented to crucially contribute to these pathologies. However, the detailed molecular events around the PERK-ATF4 pathway in β-cell pathologies still remain to be investigated. Here, we identified that ATF4 transcriptionally increases PDE4D's expression, which in turn leads to β-cell dysfunction via downregulation of cAMP signaling. Continuous expression of ATF4 specifically in β-cell produced early β-cell dysfunction and loss recapitulating the progression of type 2 diabetes in an accelerated fashion. ATF4 expression, not CHOP, induced the expression of PDE4D transcript, which resulted in diminished cAMP signaling and the blunted response to incretin and glucose. Similarly, β-cells of diabetic mice deficient of leptin receptor (BKS-db) also exhibited elevated PDE4D transcription along with defective β-cell function. Moreover, the inhibition of PDE4D activity using specific inhibitors markedly ameliorated β-cell pathologies both in BKS-db and β-cell specific ATF4 transgenic mice. Collectively, our results suggest that ATF4-mediated PDE4D expression plays a crucial role in β-cell pathologies and can be highly valuable therapeutic target to protect β-cell function during the progression of type 2 diabetes.