

## ABSTRACTS

# High glucose triggers multiple cellular stress signaling in pancreatic $\beta$ -cells and potentiate proinflammation and $\beta$ -cell dysfunction

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### Abstract

**Introduction:** Pancreatic  $\beta$ -cells are highly susceptible to high glucose-induced metabolic stress and  $\beta$ -cell dysfunction is emerging as an early event in the etiology of type 2 diabetes. The current study investigated the effects of high glucose-induced multiple cellular stress signaling that could promote proinflammation and  $\beta$ -cell dysfunction. The study also tested the effect of metformin, lactoferrin and tauroursodeoxycholic acid (TUDCA, an inhibitor of ER stress) in providing protection for  $\beta$ -cells.

**Methods:** Experiments were done using INS1  $\beta$ -cells, one of the most physiologically relevant  $\beta$ -cell models currently used to study the molecular aspects of  $\beta$ -cell dysfunction. INS1  $\beta$ -cells were propagated either in 5 mM glucose or in 25 mM glucose treatment for 24 hrs. Cells were also treated with metformin, lactoferrin or TUDCA in a hyperglycemic milieu for 24 hrs. A battery of molecular and physiological investigations were performed, which include mRNA expression of endoplasmic reticulum (ER) stress, senescence and inflammatory markers, protein expression markers, expression levels of miR-146a and its mRNA targets, intracellular reactive oxygen species (ROS) generation, intracellular  $\text{Ca}^{2+}$  levels and glucose stimulated insulin secretion (GSIS).

**Observations:** INS1  $\beta$ -cells when challenged with high glucose exhibited significantly ( $P < 0.05$ ) increased mRNA levels of ER stress (GRP78, CHOP, IRE1, PERK, XBP1), senescence ( $\beta$ -gal, P16, P21, P53) and proinflammatory signatures (IL-6, TNF $\alpha$ , MCP1, NF- $\kappa$ B, SCS3) along with altered levels of protein expression markers viz., GRP78, P53 and TNF $\alpha$ . These cells also exhibited significantly increased ROS and  $\text{Ca}^{2+}$  levels as well as decreased expression of miR-146a and impaired insulin secretion. Interestingly,  $\beta$ -cells treated with metformin, lactoferrin or TUDCA resisted all of these high glucose-mediated stress responses in a concerted and inter-linked way, and cells were also safeguarded with appropriate glucose-stimulated insulin secretion.

**Conclusion:** The study has unraveled the molecular basis for the proinflammation and impaired insulin secretion in  $\beta$ -cells that could arise from multiple cellular stress signaling viz., ER stress and senescence. While emphasizing the additional benefits of metformin, the study also exposed lactoferrin and TUDCA as novel and newer therapeutic tools, as they seem to protect  $\beta$ -cells from metabolic stress and ensure appropriate insulin secretion.

Keywords:  $\beta$ -cells, metabolic stress, inflammation, insulin

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