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Abstract P2116: Hyperglycemia Mediated Changes In A Human Cardiomyocyte Cell Model

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Abstract

Introduction: Hyperglycemia-mediated cardiac dysfunction is a critical initiator in the development of vascular complications, which, in turn, leads to cardiac fibrosis. In this study, we investigated the role of the Hippo signaling pathway in cardiomyocytes to study the complex signaling network of YAP1/TAZ on fibrotic and vascular inflammatory mediators in hyperglycemic condition. This in-vitro study demonstrated that YAP1/TAZ signaling is highly activated in the hyperglycemic cardiomyocytes. To further investigate the differentially expressed genes that are related to inflammation and fibrosis, RNA-sequencing studies were employed.

Methods: To investigate the effects of hyperglycemia-mediated changes in cardiomyocytes, we used human AC16 cells cultured in-vitro under normoglycemic (5 mM D-Glucose) and hyperglycemic (50 mM D-glucose) conditions. After 24-hours of hyperglycemic insult, cells were collected and processed for RNA-seq studies. Furthermore, we also performed Western Blot analysis to evaluate the protein expression of YAP1/TAZ under hyperglycemia induced stress conditions.

Results: Our study showed a significant upregulation of the protein expression of the YAP1/TAZ pathway in hyperglycemic cardiomyocytes. RNA-seq studies revealed differentially expressed genes (DEG) in the hyperglycemic condition in comparison with the normoglycemic condition. Among the extracellular matrix proteins, the following ECM and related markers were significantly upregulated including MMP3, TNC, TGF-beta1 and 2, COL4A1, FN1 and FGF-2. Altered expression of inflammatory mediators included the following markers, IL-6, CXCL10, CXCL12, CCL2 and VEGF-C. In addition, the following transcriptional co-activators were also significantly upregulated, including EPHA2 and MYOCD.

Conclusions: This study suggests that changes in YAP1/TAZ signaling increases vascular inflammation in response to hyperglycemia. This also leads to increased expression of inflammatory mediators as shown by our results. Thus, the inhibition of the YAP1/TAZ pathway may prevent and improve hyperglycemia associated vascular damage and inflammation.