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High Glucose Suppresses Cardiomyocyte Progenitor Cell Regenerative Capacity and the Role of miR-195/EZH2 Crosstalk in Gestational Diabetes Mellitus

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Abstract

Background

Gestational diabetes mellitus (GDM) is associated with a five-fold increase in congenital heart defects. It is critical to determine the effects of GDM *in vivo* and high glucose *in vitro* on neonatal cardiomyocyte progenitor cell (nCPCs) regenerative capacity. We sought to investigate the roles of Mir-195 and its hypothesized target gene, EZH2 in GDM.

Methods: We subjected nCPCs *in vitro* to increasing glucose concentrations and assessed cellular proliferation, migration, and secretome quality. Our *in vivo* experiments involved injecting female mice with streptozocin and pairing them with non-diabetic male mice. Progenitor cells from resultant embryos at E14.5 were evaluated for viability, proliferation, ROS generation and apoptosis. mRNA expression levels of Mir-195 and EZH2 protein levels were detected using RT-qPCR and western blot analysis respectively.

Results: Subjecting nCPCs *in vitro* to increased glucose concentration led to increased % cell death, decreased proliferation and expression of paracrine factors (Figure 1). Our *in vivo* models showed decreased expression of c-kit+/Lin- cells (0.2% v 2.8%; $p<0.05$) and ISL1+ cells (24% v 51%; $p<0.05$) and increased dihydroethidium positivity in DM-nCPCs at E14.5 (65% v 57%; $p<0.05$). Expression of Mir-195 was higher in DM-nCPCs (Figure 2) but EZH2 mRNA and protein expression levels were significantly decreased.

Conclusion: The viability of DM-nCPCs both *in vivo* and *in vitro* is decreased compared to NDM-nCPCs suggesting decreased postnatal regenerative capacity and poorer secretome quality. Mir-195 is associated with increased apoptosis and decreased proliferation of nCPCs via abrogation of the protective effects of EZH2. Mir-195 is a target for future therapeutics aimed at ameliorating GDM.

Keywords: Cardiomyocyte progenitor cells, gestational diabetes mellitus, micro-RNA

Funding and Conflicts of Interest

None to disclose