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Abstract 465: A 3D Bioprinted Human Cardiac Cell Platform to Model the Pathophysiology of Diabetes

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Abstract

Type-II diabetes (T2D) patients affected by underlying hyperglycemic (high glucose/blood sugar) conditions often suffer from cardiac atrophy, resulting in tissue mass reduction and debilitating cardiac health. To understand pathophysiological mechanisms during progression of cardiac atrophy, a 3D bioprinted organoid platform was developed from a mixture of hydrogels containing human cardiac cells, including cardiomyocytes (CM), fibroblasts (CF) and endothelial cells (EC), to mimic the functionality of the in-vivo tissue. The organoids were cultured using normoglycemic- or hyperglycemic-conditions. The expression of essential biomarkers in these organoids, for myocardin (Myocd), troponin-I (TRP-I), fibroblast protein-1 (FSP-1) and endothelin-1 (ET-1) was confirmed. To assess the physiological cellular connections during hyperglycemia, the presence of Connexin-43 (CX-43) was assessed in the presence of a CX-43 blocker, gap26. Epigenomic tools were used to simultaneously interrogate histone-modifications by histone 3 lysine 9 mono-methylation (H3K9me1) along with the co-regulation of inflammatory mediators, such as the high mobility group box 1 (HMGB1) and toll like receptor 4 (TLR4) in the cardiac organoids cultured using normal versus hyperglycemic conditions. Organoids exposed to high glucose showed an increased expression of H3K9me1 as well as inflammatory mediators HMGB1 and TLR4. Hyperglycemia also exhibited alterations in expression of Myocd and FSP-1 in the organoids, compared to normoglycemic conditions. Treatment with gap26 affected the CX-43 expression significantly, in organoids cultured under hyperglycemia suggesting that high glucose conditions associated with prolonged diabetes may lead to compromised CM-CF coupling, essential for maintenance of cardiac functionality. Increased levels of H3K9me1 suggest decreased expression of Myocd, which may lead to CM degeneration. Epigenetic modifications including alterations in histone methylation in regulation of the myocardial genes and gap junction proteins under hyperglycemic conditions, may lead to cardiac atrophy. We expect to establish an actual T2D patient iPSC cell derived cardiac platform, to offer new therapeutic opportunities within the field.

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