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MicroRNA-210 mediates PKCδ-dependent upregulation of JNK to cause cardiac mitochondrial damage and apoptosis following advanced glycation end-products exposure

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Background: Hyperglycemia results in the formation of advanced glycation end products (AGEs), which can induce reactive oxygen species (ROS) production leading to diabetic cardiomyopathy. Our previous study showed that AGE induced ROS-dependent apoptosis is mediated via the protein kinase C (PKC) δ-enhanced mitochondrial damage in cardiomyocytes. MicroRNA-210, a regulator of mitogen-activated protein kinase-JNK (JNK), which is a downstream of PKCδ, has been reported to play a role to mediate mitochondrial function. Therefore, we hypothesized that miR-210 mediates PKCδ-dependent upregulation of JNK to cause cardiac mitochondrial damage and apoptosis following AGE exposure.

Methods & Results: Cardiac miR-210 and mitochondria function were down regulated following AGE exposure. Furthermore, JNK was up-regulated and involved in AGE-induced mitochondrial damage. Interestingly, the result of luciferase activity of the miR-210 mimic treatment was significantly lower than control and was reversed following the inhibitor treatment, indicating JNK is a target of miR210. Moreover, JNK activation induced by AGEs was reduced by the treatment of miR-210 mimic and reversed by the treatment of miR-210 inhibitor, indicating the regulation function of miR-210 for JNK activation following AGE exposure. Additionally, the JNK-dependent mitochondrial dysfunction was reversed following the treatment of miR210 mimic, and miR210 inhibitor showed no effect on JNK-induced mitochondrial dysfunction in AGE-exposed cardiomyocytes.

Conclusion: PKCδ enhanced JNK-dependent mitochondrial damage is mediated through the reduction of miR210 in cardiomyocytes following AGE exposure. Additionally, the JNK-dependent mitochondrial dysfunction was reversed following the treatment of miR210 mimic, and miR210 inhibitor showed no effect on JNK-induced mitochondrial dysfunction in AGE-exposed cardiomyocytes.

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