Role of SGLT1 in high glucose level-induced MMP-2 expression in human cardiac fibroblasts

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学 位 論 文 の 要 旨

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学位論文題目	Role of SGLT1 in high glucose level-induced MMP-2 expression in human cardiac fibroblasts （高グルコース誘発性ヒト心臓線維芽細胞 MMP-2 発現における SGLT1 の役割）		

【Objective】

Cardiac fibrosis is one of the major pathological manifestations of diabetic cardiomyopathy (DCM), leading to cardiac remodeling, dilated cardiomyopathy, and congestive heart failure. Human cardiac fibroblasts (HCF) constitute the predominant cell type in the heart, and matrix metalloproteinases (MMPs)/tissue inhibitor of metalloproteinases (TIMPs) are involved in cardiac fibrosis. However, it is unclear whether high glucose levels affect the expression of MMPs/TIMPs in HCF. Over years, sodium-glucose cotransporter (SGLT) inhibitors have been developed as novel therapeutic agents, and the anti-DCM effect of SGLT inhibitors has been shown by some studies. Whether SLGT inhibitors can protect the diabetic heart by directly inhibiting the SGLTs in HCF, in addition to lowering the blood glucose levels, has not been determined. In this study, we are going to explore the role of SGLT1 in high glucose level-induced MMP-2 expression in human cardiac fibroblasts.

【Methodology】

The cells were divided into 6 groups: Control group, Glu 30 mM group, Phlorizin 10 μM group, Phlorizin 100 μM group, Dapagliflozin 10 μM group, and Dapagliflozin 100 μM group. After group-specific treatment, RT-PCR was used to test the mRNA expression of MMP-2, TIMP-1, TIMP-2, and SGLT-1. Western blot was used to test the relative expresion of SGLT1 in each group.

【Results】

In this study, increased MMP-2 expression was noted in the HCF in response to high glucose levels, which could be reversed by phlorizin (inhibits both SGLT1 and SGLT2), but not dapagliflozin (inhibits SGLT2). In addition, SGLT1 was found to be present in the HCF, and high glucose level was found to increase SGLT1 expression, which could be attenuated by phlorizin.

【Discussion】

Myocardial fibrosis is the most frequently proposed mechanism to explain cardiac changes in DCM. Cardiac fibroblasts are the main cell type constituting the heart, and are responsible for the basal deposition and degradation of the ECM. As the primary structural cells of the heart, cardiac fibroblasts are critically involved in all cardiac fibrotic conditions. In this study, we found that high levels of glucose can induce MMP-2 expression in the HCF.

MMP-2 is the primary kind of gelatinases that can degrade the ECM. Synthesis and decomposition of ECM are ongoing processes. In the normal heart, the decomposition and synthesis of ECM are in dynamic equilibrium. The balance is maintained by MMPs and TIMPs. As TIMP-2 is an important member of the TIMP family, it can effectively inhibit the activity of MMP-2. Therefore, we further determined the MMP-2/TIMP-2 ratio and found that high glucose

level also increases this ratio. Thus, these results indicate that high glucose levels can degrade the ECM. Derangement of MMP-2 expression and activity alters the balance between ECM synthesis and degradation, resulting in excessive collagen deposition and reduced structural integrity in the myocardium. Increasing degradation of ECM supplies space for the proliferation and migration of HCF and other macrophagocytes, which secrete inflammatory and growth factors, further enhancing the cardiac remodeling process.Therefore, we suggest that high glucose levels up-regulate the expression of MMP-2, which further promotes ECM degradation, increased HCF migration and proliferation, finally resulting in fibrosis and DCM.

In the heart, SGLT1 has been shown to be expressed in the cardiomyocytes and endothelial cells. In this study, we found that SGLT1 was expressed in HCF. This is, to the best of our knowledge, the first report that SGLT1 is present in HCF. In addition, we found that SGLT1 is up-regulated by glucose levels. In order to explore the effect of SGLT1, we used phlorizin (inhibits SGLT1 and SGLT2) and dapagliflozin (inhibits SGLT2). Our results showed that phlorizin can inhibit SGLT-1 expression in HCF. In addition, phlorizin can inhibit high glucose level-induced MMP-2 and TIMP-1 expression in HCF. Also, dapagliflozin did not exert this effect. These results indicated that the up-regulation of SGLT1 is necessary for the induction of MMP-2 expression by high glucose levels, and that the inhibition of SGLT1 can attenuate this effect. This might be the mechanism involved in the down-regulation of MMP-2 expression by inhibited SGLT1.

【Conclusion】

High glucose levels induced MMP-2 expression in the HCF, possibly by upregulating SGLT1. SGLT1 inhibition might be a new potential strategy for the treatment of DCM.

備考　1　※印の欄は、記入しないこと。

2　学位論文の要旨は、和文により研究の目的、方法、結果、考察、結論等の順に記載し、2,000 字程度にまとめタイプ等で印字すること。

3　図表は、挿入しない