Hydrogen sulfide promoted retinoic acid-related orphan receptor α transcription to alleviate diabetic cardiomyopathy

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Diabetic cardiomyopathy (DCM) is one serious and common complication in diabetes without effective treatments. Hydrogen sulfide (H_2S) fights against a variety of cardiovascular diseases including DCM. Retinoic acid-related orphan receptor α (RORα) has protective effects on cardiovascular system. However, whether RORα mediates the protective effect of H_2S against DCM remains unknown. The present research was to explore the roles and mechanisms of RORα in H_2S against DCM. Our study demonstrated that H_2S donor sodium hydrosulfide (NaHS) alleviated cell injury but enhanced RORα expression in high glucose (HG)-stimulated cardiomyocytes. However, NaHS no longer had the protective effect on attenuating cell damage and oxidative stress, improving mitochondrial membrane potential, inhibiting necroptosis and enhanced signal transducer and activator of transcription 3 (STAT3) Ser727 phosphorylation in HG-stimulated cardiomyocytes after RORα siRNA transfection. Moreover, NaHS improved cardiac function, attenuated myocardial hypertrophy and fibrosis, alleviated oxidative stress, inhibited necroptosis, but increased STAT3

phosphorylation in wild type (WT) mice but not in RORα knockout mice (a spontaneous staggerer mice, sg/sg mice) with diabetes. Additionally, NaHS increased RORα promoter activity in cardiomyocytes with HG stimulation, which was related to the binding site of E2F transcription factor 1 (E2F1) in the upstream region of RORα promoter. NaHS enhanced E2F1 expression and increased the binding of E2F1 to RORα promoter in cardiomyocytes with HG stimulation. In sum, H_2S promoted RORα transcription via E2F1 to alleviate necroptosis and protect against DCM. It is helpful to propose a novel therapeutic implication for DCM.