Endogenous hydrogen sulfide deficiency and exogenous hydrogen sulfide supplement regulates skin fibroblasts proliferation via necroptosis

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Abstract

An excessive proliferation of skin fibroblasts usually results in different skin fibrotic diseases. Hydrogen sulfide (H_2S) is regarded as an important autogenous gasotransmitter with various functions. The study aimed to investigate the roles and mechanisms of H_2S on primary mice skin fibroblasts proliferation. Cell proliferation and collagen synthesis was assessed with the expression of α-smooth muscle actin (α-SMA), proliferating cell nuclear antigen (PCNA), Collagen I and Collagen III. The degree of oxidative stress was evaluated by dihydroethidium (DHE) and MitoSOX staining. Mitochondrial membrane potential (ΔΨm) was detected by JC-1 staining. Necroptosis was evaluated with TDT mediated dUTP nick end labeling (TUNEL), and expression of receptor interacting protein kinase 1 (RIPK1), RIPK3 and mixed lineage kinase domain like protein (MLKL). The present study found that α-SMA, PCNA, Collagen I and Collagen III expression were increased, oxidative stress were promoted, ΔΨm was impaired, positive rate of TUNEL staining, RIPK1 and RIPK3 expression as well as MLKL phosphorylation were all enhanced in skin fibroblasts from cystathionine γ-lyase (CSE) knockout (KO) mice or transforming growth factor-β_1 (TGF-β_1) -stimulated skin fibroblasts, which was restored by exogenous donor sodium hydrosulfide (NaHS). In conclusion, endogenous H_2S production impairment in CSE deficiency mice accelerated skin fibroblasts proliferation via promoted necroptosis, which was attenuated by exogenous H_2S. Exogenous H_2S supplement also alleviated proliferation of skin fibroblasts with TGF-β_1 stimulation via necroptosis inhibition. This study provides evidence for H_2S as a candidate agent to prevent and treat skin fibrotic diseases.

Keywords: hydrogen sulfide, skin fibroblasts proliferation, cystathionine γ-lyase, necroptosis, oxidative stress