

Empagliflozin Ameliorates Bleomycin-Induced Pulmonary Fibrosis in Rats by Modulating Sesn2/AMPK/Nrf2 Signaling and Targeting Ferroptosis and Autophagy

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Abstract:

Pulmonary fibrosis (PF) is a life-threatening disorder that severely disrupts normal lung architecture and function, resulting in severe respiratory failure and death. It has no definite treatment. Empagliflozin (EMPA), a sodium-glucose cotransporter 2 (SGLT2) inhibitor, has protective potential in PF. However, the mechanisms underlying these effects require further elucidation. Therefore, this study aimed to evaluate the ameliorative effect of EMPA against bleomycin (BLM)-induced PF and the potential mechanisms. Twenty-four male Wister rats were randomly divided into four groups: control, BLM treated, EMPA treated, and EMPA+BLM treated. EMPA significantly improved the histopathological injuries illustrated by both hematoxylin and eosin and Masson's trichrome stained lung tissue sections, as confirmed by electron microscopic examination.

It significantly reduced the lung index, hydroxyproline content, and transforming growth factor β 1 levels in the BLM rat model. It had an anti-inflammatory effect, as evidenced by a decrease in the inflammatory

cytokines' tumor necrosis factor alpha and high mobility group box 1, inflammatory cell infiltration into the bronchoalveolar lavage fluid, and the CD68 immunoreaction.

Furthermore, EMPA mitigated oxidative stress, DNA fragmentation, ferroptosis, and endoplasmic reticulum stress, as evidenced by the up-regulation of nuclear factor erythroid 2-related factor expression, heme oxygenase-1 activity, glutathione peroxidase 4 levels, and a decrease in C/EBP homologous protein levels. This protective potential could be explained on the basis of autophagy induction via up-regulating lung sestrin2 expression and the LC3 II immunoreaction observed in this study.

Our findings indicated that EMPA protected against BLM-induced PF-associated cellular stress by enhancing autophagy and modulating sestrin2/adenosine monophosphate-activated protein kinase/nuclear factor erythroid 2-related factor 2/heme oxygenase 1 signaling.