KDM2B Exacerbates Fibrosis After Myocardial Infarction by Regulating the Expression of GDF9 from Macrophage

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Abstract

In various cardiac pathologies, excessive fibrosis represents a central driver of adverse remodeling and dysfunction that culminates in heart failure. Histone methylation has been implicated in diverse pathophysiological processes, yet the contribution of histone methylation-modifying enzymes to pathological cardiac fibrosis remains incompletely understood. Here, we identify lysine-specific demethylase 2B, KDM2B, as a critical epigenetic regulator of pathological cardiac fibrosis. We generated KDM2B knockout mice via CRISPR-Cas9, established myocardial infarction models, assessed cardiac function, performed macrophage-fibroblast co-culture, used RNA-seq, qPCR, and western blot to validate KDM2B regulation of GDF9, and confirmed effects on fibroblast behavior via exogenous GDF9. KDM2B expression is upregulated in myocardial tissues under pathological stress, and its deficiency substantially attenuates cardiac fibrosis, preserves cardiac function, and prevents adverse remodeling following myocardial infarction. Genetic ablation or pharmacological inhibition of KDM2B restricts the differentiation of cardiac fibroblasts into fibrogenic myofibroblasts and suppresses the fibrotic response, while also promoting an endothelial-like phenotype and enhancing angiogenesis after myocardial injury. Mechanistically, KDM2B deficiency relieves repression of growth differentiation factor 9 in myeloid cells, thereby enhancing SMAD-dependent transforming growth factor-β signaling and the expression of fibrosis-promoting genes. Collectively, these findings establish KDM2B as a pathogenic driver of cardiac fibrosis and a potential therapeutic target for cardiac dysfunction and heart failure.

Keywords

Myocardial Infarction, Cardiac Fibrosis, KDM2B, Macrophage, GDF9