KDDF
Korea Drug Development Fund

Asset #7
Duke-NUS Medical School

Targeting WWP2 for Treating Diseases Characterized by Fibrosis

Therapeutic Area	Cardiovascular Disease, Nephrology	**Indications**	Heart and Kidney Fibrosis
Modality	Small Molecule	**Development Stage**	Pre-clinical

Overview

Background

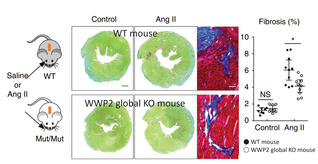
- Tissue fibrosis arises from disrupted tissue healing, resulting in harmful scar tissue formation. Despite progress, effective and safe cures for fibrosis-related disorders are lacking, causing significant global health and economic burdens.
- Common fibrotic diseases (e.g., atherosclerosis, cirrhosis, pulmonary fibrosis) lack preventive treatments, and current therapies with anti-inflammatory and immunosuppressive drugs lack specificity and may induce toxicity. Thus, unmet needs persist in achieving effective and safe fibrosis therapies.

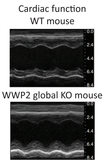
Technology Advantages

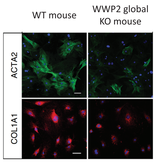
- Specific Drug Target: WWP2 identified as validated drug target for fibrosis treatment in heart, kidney and lung tissues
- Bioinformatics Insight: Bioinformatics analyses revealed WWP2's role in regulating pro-fibrosis molecular network
- In vitro and in vivo validations: Studies confirmed WWP2's significance in regulating matrix accumulation in cardiac and kidney fibrosis, and WWP2 anti-inflammatory function
- Novel Therapeutic Target: N-terminal of WWP2 recognized as potential druggable target
- Clinical Potential: Ongoing pre-clinical testing of small molecule compounds for lead identification

Key Data

WWP2 regulates pathological cardiac fibrosis via its action in fibroblasts and macrophages

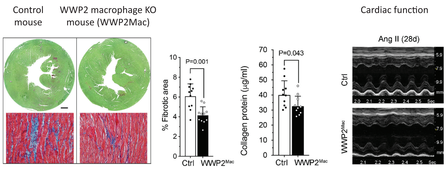




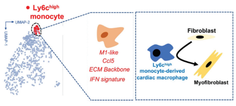


Representative microscopy images with immunostaining for ACTA2 and COL1A1 after TGFβ1 stimulation in WT and WWP2 KO cardiac myofibroblasts

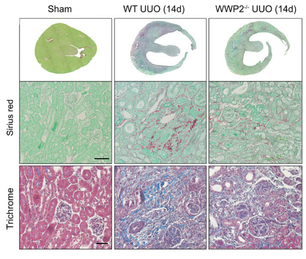
Left, Representative Sirius red & Masson's Trichrome staining of short-axis sections in LV (Scale bar: 0.5 mm). Right, Quantification of fibrosis area in transverse histological sections by Sirius red staining at the mid-ventricle. Representative M-mode echocardiograms (middle LV long-axis) in WT and WWP2 KO mice after heart injury. Top panels: global WWP2 KO; Bottom panels: macrophage-specific WWP2 KO



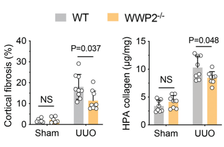
After injury, WWP2 regulates Ly6chigh monocytes via Ccl5, WWP2 controls macrophage infiltration & activation, and myofibroblast trans-differentiation



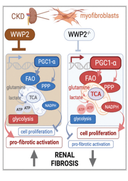
WWP2 regulates the metabolic reprogramming of renal myofibroblasts to promote kidney fibrosis in chronic kidney disease (CKD)



Reduced cortical fibrosis-positive area (left, %) and HPA collagen levels (right, μg/mg) in WWP2 KO mouse (WWP2-/-) kidneys compred with WT following UUO-induced fibrosis model at 14 days. n = 6-10 mice, in each group.



WWP2 regulatory mechanism of kidney fibrosis and myofibroblasts metabolism



Metabolic reprogramming of myofibroblasts

WWP2 regulates PGC-1a, and the associated metabolic alterations in kidney fibrosis

Representative images of WT and WWP2-/- (WWP2 global KO) mouse kidneys following UUO model for 14 days. (n=8 for each condition). Top and middle panels, Sirius Red staining for whole section and representative fibrotic area. Scale bars, 50 μm. Bottom panels, representative images of Masson's trichrome staining for representative fibrotic area. Scale bars, 20 μm.

IP Status & Publication(s)

Intellectual Property

Patent Number
PCT-EP2020-066260 (2020.06.12)

Patent Family
PCT, US, EP, CN

Publication(s)

- Chen et al. (2019). WWP2 regulates pathological cardiac fibrosis by modulating SMAD2 signaling. Nature Communications
- Chen et al. (2022). The E3 ubiquitin ligase WWP2 regulates pro-fibrogenic monocyte infiltration and activity in heart fibrosis. Nature Communications
- Chen et al. (2023). WWP2 mediates the metabolic reprogramming of renal myofibroblasts to promote kidney fibrosis. bioRxiv 2023.08.22.554242; doi: https://doi.org/10.1101/2023.08.22.554242