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Glutamyl-prolyl-tRNA-synthetase 1 regulates kidney fibrosis by controlling STAT3 and mitochondrial dysfunction

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Objectives: Glutamyl-prolyl-tRNA synthetase 1 (EPRS1), an enzyme necessary for synthesizing proline-rich profibrotic proteins such as collagen, is known to be involved in various fibrotic diseases. This study aims to identify the results of the genetic deletion of *EPRS1* and prove that EPRS1 can be involved in kidney fibrosis.

Methods: To examine the kidney effects of EPRS1 inhibition, we used folic acid (FA)-induced chronic kidney disease (CKD) model in EPRS1 heterozygous knockout (C57BL/6 EPRS1^{tm1b}, *Eprs1*$^{+/-}$) mice and wild-type mice. Additionally, we tested EPRS1 inhibition genetically in HK-2 cells to determine if it played a role in fibrosis inhibition and mitochondrial dysfunction.

Results: FA-induced kidney fibrosis, mitochondrial dysfunction, increased blood urea nitrogen and serum creatinine, and upregulated EPRS1 expression were observed in wild-type CKD mice. *Eprs1*$^{+/-}$ mice decreased EPRS1 levels, kidney fibrosis, and mitochondrial dysfunction. Moreover, *Eprs1*$^{+/-}$ mice effectively inhibited both extracellular matrix marker (Collagen 1A1) and the levels of SIRT1/STAT3. Similarly, the genetic inhibition of *EPRS1* in transforming growth factor-β1-induced HK-2 cells inhibited fibrosis by suppressing p-STAT3 and activating SIRT1/PGC-1α and improving mitochondrial dysfunction. Similarly, the genetic inhibition of *EPRS1* in transforming growth factor-β1-induced HK-2 cells inhibited fibrosis by suppressing p-STAT3 and activating SIRT1/PGC-1α. Genetic inhibition of *EPRS1* also improved mitochondrial dysfunction.

Conclusions: Our results indicate for the first time an increased expression of EPRS1 in kidney fibrosis and that EPRS1 inhibition could be effective by regulating mitochondrial dysfunction and p-STAT3 signaling in chronic kidney disease.