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Research Paper

The program of renal fibrogenesis is controlled by microRNAs regulating oxidative metabolism

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ABSTRACT

Excessive accumulation of extracellular matrix (ECM) is the hallmark of fibrotic diseases. In the kidney, it is the final common pathway of prevalent diseases, leading to chronic renal failure. While cytokines such as TGF-β play a fundamental role in myofibroblast transformation, recent work has shown that mitochondrial dysfunction and defective fatty acid oxidation (FAO), which compromise the main source of energy for renal tubular epithelial cells, have been proposed to be fundamental contributors to the development and progression of kidney fibrosis. MicroRNAs (miRNAs), which regulate gene expression post-transcriptionally, have been reported to control renal fibrogenesis. To identify miRNAs involved in the metabolic derangement of renal fibrosis, we performed a miRNA array screen in the mouse model of unilateral ureteral obstruction (UUO). MiR-150-5p and miR-495-3p were selected for their link to human pathology, their role in mitochondrial metabolism and their targeting of the fatty acid shuttling enzyme CPT1A. We found a 2- and 4-fold upregulation of miR-150-5p and miR-495-5p, respectively, in both the UUO and the folic acid induced nephropathy (FAN) models, while TGF-β1 upregulated their expressions in the human renal tubular epithelial cell line HKC-8. These miRNAs synergized with TGF-β regarding its pro-fibrotic effect by enhancing the fibrosis-associated markers Acta2, Col1α1 and Fn1. Bioenergetics studies showed a reduction of FAO-associated oxygen consumption rate (OCR) in HKC-8 cells in the presence of both miRNAs. Consistently, expression levels of their mitochondrial-related target genes CPT1A, PGC1α and the mitochondrial transcription factor A (TFAM), were reduced by half in renal epithelial cells exposed to these miRNAs. By contrast, we did not detect changes in mitochondrial mass and transmembrane potential (ΔΨm) or mitochondrial superoxide radical anion production. Our data support that miR-150 and miR-495 may contribute to renal fibrogenesis by aggravating the metabolic failure critically involved in tubular epithelial cells, ultimately leading to fibrosis.

1. Introduction

Chronic kidney disease (CKD) is a clinical condition where the reduction of renal function is maintained. It is generally considered to be irreversible and progressive. It represents an important public health problem that can affect 12–14% of the general population [1]. It may be present in about 30–40% of patients with highly prevalent pathologies such as diabetes mellitus and hypertension, where it contributes to dictate evolution and prognosis. Regardless of the disease etiology, progression of CKD leads to tubule-interstitial and glomerular fibrosis

Abbreviations: ECM, extracellular matrix; FAO, fatty acid oxidation; miRNAs, microRNAs; FAN, folic acid nephropathy; UUO, unilateral ureteral obstruction; TFAM, mitochondrial transcription factor A; OCR, oxygen consumption rate; CKD, chronic kidney disease; TGF-β, transforming growth factor-β; AKI, acute kidney injury; FBS, fetal bovine serum; ITS, insulin-transferrin-selenium; SPF, specific pathogen free; FDR, false discovery rate; ECAR, extracellular acidification rate; Eto, etomoxir; MMP, mitochondrial membrane potential; ETC, electron transport chain; EMT, epithelial-to-mesenchymal transition.

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