Unraveling New Mechanisms of Renal Fibrosis With Potential Therapeutic Implications

Francisco Maduell, Nuria Garcia-Fernandez, Joaquín Manrique, Arantxa González, Javier Díez

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Disease-related injury in any organ triggers a complex cascade of cellular and molecular responses that culminates in tissue fibrosis. When this process progresses for a prolonged period of time, parenchymal scarring and ultimately cellular dysfunction and organ failure ensue. In this conceptual framework, renal fibrosis corresponds to the replacement of renal functional tissue by extracellular matrix proteins, mainly fibrillary collagens, which lead to chronic kidney disease (CKD) and ultimately to chronic kidney failure that represents the end-stage renal disease. The concept of reversing CKD has been intensively researched during the past decade. Indeed, because the prevalence of end-stage renal disease is constantly on the rise, the lack of established antifibrotic therapies is a considerable unmet need in clinical practice. To date, the possibility of effective antifibrotic treatment has been established in experimental models of CKD, and although multiple antifibrotic compounds targeting various components of the fibrotic pathway are being assessed in clinical trials, the available results show that they are ineffective or only slightly successful to prevent or reverse renal fibrosis. Hence, it is essential to understand the pathogenesis of renal fibrosis and to discover and better understand new strategies for treating this lesion from its earliest phases.

As in other organs, the mechanistic hallmark of renal fibrosis is the accumulation of a large number of matrix-producing cells or myofibroblasts. These cells are derived from diverse origins, such as resident fibroblasts, vascular pericytes, epithelial-to-mesenchymal transition, and bone marrow (circulating fibrocytes). Recently, endothelial-to-mesenchymal transition (EndoMT) or endothelial-to-myofibroblast transition has been also recognized as a novel mechanism for the generation of myofibroblasts and induction of fibrosis in the kidney.[1] Several autocrine or paracrine signaling molecules can induce EndoMT, including the TGF-β (transforming growth factor-β) superfamily of proteins, inflammatory cytokines, vasoactive amines and peptides, and reactive oxygen species.[2] On the contrary, several growth factors (eg, vascular endothelial growth factor-A) and some microRNAs (eg, miR-155) appear to be negative regulators of EndoMT.[2] Additionally, several pharmacological agents that among other actions inhibit EndoMT (eg, linagliptin, relaxin, cinacalcet, losartan, and spironolactone) have been proposed as potential therapeutic agents to reduce organ fibrosis.[2]

Preliminary data suggest that sirtuins can also regulate EndoMT. Sirtuins comprise a highly conserved family of proteins encoded by the silent information regulator 2 genes. Mammalian SIRT1-7 (sirtuins1-7), also called class III histone deacetylases, are a family of 7 nicotinamide adenine dinucleotide-dependent deacetylases, which perform nonredundant functions in adapting physiology to environmental stressors, namely through chemical reversal of acetyllysine modifications of cellular proteins. Accumulating evidence indicates the beneficial effects of sirtuins, including SIRT1 and SIRT3, in kidney pathophysiology.[3] SIRT3 is a nuclear DNA-encoded 44 kDa sirtuin localized in the mitochondrial matrix that acts as a master regulator of mitochondrial function by activating a wide range of targets involved in ATP production, energy metabolism, antioxidant pathway, and mitochondrial dynamics.[4]

Beyond its involvement in maintaining mitochondrial integrity, a growing body of evidence points to SIRT3 as a protective agent against fibrosis developed in response to aging and tissue injury. It has been reported that SIRT3 KO (knockout) mice with age develop fibrosis in the kidney, the heart, and other organs, whereas systemic SIRT3-overexpressing mice do not.[5] Of interest, SIRT3 deficiency caused induction of TGF-β expression and signaling in fibrotic organs.[5] In the current issue of the journal, Lin et al[6] provide a convincing new piece of knowledge on the role of SIRT3 in regulating renal fibrosis through EndoMT for which they deserve to be congratulated. Lin et al[6] used the in vivo Ang II (angiotensin II)–induced hypertensive renal injury model, characterized by reduced SIRT3 expression, increase of reactive oxygen species, and activation of EndoMT and fibrosis. In experiments performed in *Sirt3* KO mice and in SIRT3 endothelial cell–specific transgenic mice, the authors observed that low SIRT3 exacerbates and high SIRT3 reduces renal reactive oxygen species, EndoMT, fibrosis, and dysfunction induced by chronic Ang II infusion. In addition, the improvement in renal parameters observed in SIRT3 endothelial cell–specific transgenic mice was not associated with changes in blood pressure.

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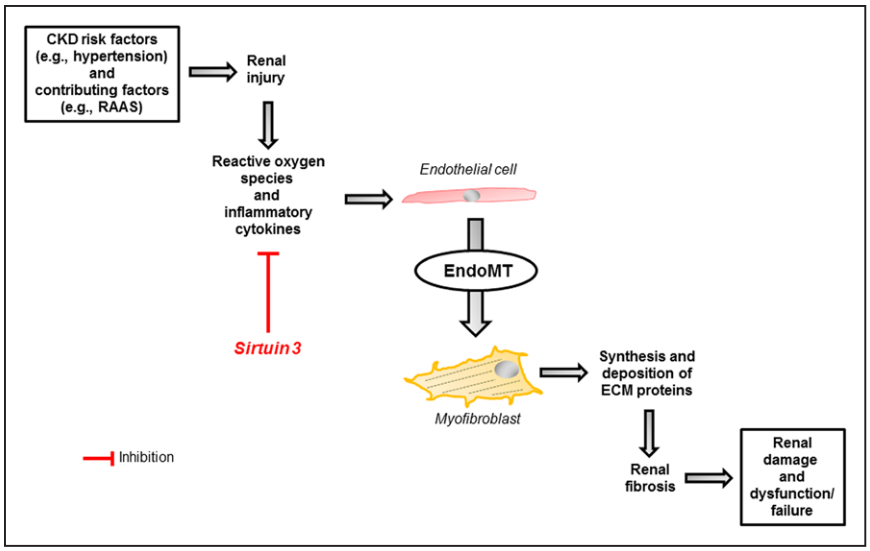

Figure. Schematic representation of the involvement of endothelial-to-mesenchymal transition (EndoMT) in the process of renal fibrosis, and the proposed mechanism of action of sirtuin 3 to interfere with this process. Sirtuin 3 may prevent EndoMT by reducing the availability of reactive oxygen species (eg, via activation of the antioxidant enzyme Foxo3a-dependent catalase) or by inhibiting the inflammatory response (eg, via blockade of the TGF-β [transforming growth factor-β]–Smad3 pathway). CKD indicates chronic kidney disease; ECM, extracellular matrix; and RAAS, renin–angiotensin–aldosterone system.

Additionally, in in vitro experiments, Lin et al[6] found that the ability of Ang II to induce EndoMT and reduce catalase expression in normal mouse glomerular endothelial cells was abrogated in glomerular endothelial cells overexpressing SIRT3. Of interest, SIRT3 overexpression was associated with deacetylation and nuclear localization of Foxo3a and subsequent activation of Foxo3a-dependent catalase expression. Collectively, these findings suggest that SIRT3 may play a protective role against Ang II–induced renal fibrosis and dysfunction through the inhibition of EndoMT (Figure). Furthermore, the authors provide evidence suggesting a role for the activation of Foxo3a-catalase antioxidant pathway as a mechanism potentially involved in the inhibition of EndoMT by SIRT3.

The information provided by Lin et al[6] sets the stage for the pharmacological activation of SIRT3 to gain advantage of its antifibrotic renal actions. In this regard, it has been reported that honokiol—a natural biphenolic compound that activates SIRT3—blocks cardiac fibroblast proliferation and differentiation to myofibroblasts in a SIRT3-dependent manner[7] and reduces cardiac reactive oxygen species and fibrosis in doxorubicin-induced cardiomyopathy in mice.[8] In another study, it has been shown that SIRT3 activation induced by the polyphenolic compound resveratrol suppressed Ang II–induced differentiation of cardiac fibroblasts into myofibroblasts through the TGF-β/Smad3 pathway.[9] Additional studies are required to test the renal antifibrotic efficacy of these compounds in fibrogenic renal cells and animal models of renal disease.

The translational perspective of this approach is given by the observation that SIRT3 protein expression was reduced in peripheral blood mononuclear cells from hypertensive patients compared with normotensive subjects.[10] Furthermore, SOD2 (superoxide dismutase 2) acetylation—an inverse index of SIRT3 activity—was higher in cells from hypertensive patients than in cells from normotensive subjects.[10] Therefore, it can be hypothesized that the measurement of SIRT3 expression and SOD2 acetylation in peripheral blood mononuclear cells may help to identify patients who may benefit from targeting SIRT3.

CKD is a systemic disease, and as such, renal fibrosis is associated with fibrosis in other organs (eg, heart and blood vessels). Furthermore, the process leading to renal fibrosis in CKD shares many features in common with the fibrotic response in other organs. The challenge is, therefore, to find those generic antifibrotic strategies that have potential to ameliorate progression in multiple organs, that is, the overlap. In this conceptual framework, stimulation of SIRT3 emerges as a promising strategy to be tested, namely in patients with CKD with low expression and activity of this protein in peripheral blood mononuclear cells.

Disclosures

None.

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