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Hrd1 participates in the regulation of collagen I synthesis in renal fibrosis

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Abstract The production and accumulation of collagen-rich extracellular matrix are common hallmarks during the process of renal fibrogenesis. However, the mechanisms of the regulation of collagen synthesis in renal fibrosis are still unclear. Hrd1, an E3 ubiquitin ligase, plays important roles for protein folding in ER and transport to Golgi. Here, we examined the hypothesis that Hrd1 posttranslationally regulates collagen synthesis in renal interstitial fibrogenesis. Unilateral ureteral obstruction induced Hrd1 expression, predominantly in the renal interstitium and tubular epithelium of fibrotic kidneys. Transforming growth factor β1, as a key mediator in kidney fibrosis, significantly increased the expressions of Hrd1, α-smooth muscle actin, fibronectin as well as procollagen I and mature collagen I in dose-dependent manner in tubular epithelial cells, suggesting that collagen I maturation might be modulated during renal fibrosis. In cultured renal fibroblasts, Hrd1 knockdown decreased secreted collagen I ~60 % in the supernatant of NRK-49F cells. Conversely, Hrd1 overexpression increased secreted collagen I ~1.5-fold. Hrd1 overexpression significantly increased the expressions of both procollagen I and mature collagen I, ~2.2-fold and ~1.8-fold, respectively. However, Hrd1 knockdown markedly decreased the expression of mature collagen I ~80 %, while procollagen I expression only was decreased ~21 %. Moreover, short interfering RNA-induced knockdown of Sec23A blunted the increase in collagen I expression (both immature and mature form) by Hrd1 overexpression and returned collagen I expression toward control levels. These results indicate that Hrd1 plays an important role in the maturation of collagen I in renal fibrosis, and that Sec23A pathway is required for ER-to-Golgi procollagen trafficking to promote collagen synthesis.

Keywords Hrd1 · Collagen I · E3 ubiquitin ligase · Renal fibrogenesis · Unilateral ureteral obstruction

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Introduction

Renal fibrosis is the final common pathway of virtually all kidney diseases leading to chronic renal failure [1, 2]. Production and deposition of a large amount of extracellular matrix (ECM) components are major cellular events of tubulointerstitial fibrosis in both animals and humans [3, 4]. Type I collagen, as well as fibronectin and type III collagens, is known as interstitial matrix components. However, the mechanisms governing the regulation of ECM metabolism during renal fibrosis are only incompletely defined.

Collagens are the most abundant proteins in mammals, constituting ~30 % of its protein mass [5]. To date, at least 27 collagen types have been identified. Prochop and Kivirikko [6] classified these collagen proteins into five subfamilies: (1) fibril-forming collagens, (2) network-forming collagens, (3) fibril-associated collagens with interrupted triple helices (FACITs), (4) transmembrane collagens, and (5) other types of collagens. Among them, type I collagen (collagen I) is a typical fibril-forming collagen and plays various roles as a major component of ECM [5, 7].

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