

The Critical Role of EGFR in Hyperuricemia Nephropathy

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Abstract

Uric acid is the final metabolic product of purine metabolism in humans due to a lack of the enzyme uricase. The increased level of serum uric acid is tightly related to many diseases, such as hypertension, hyperlipidemia, atherosclerosis, coronary heart disease and diabetes. Hyperuricemia has also been considered as an independent risk factor in the progression of hyperuricemic nephropathy. Currently, it remains incompletely clear about the underlying mechanism by which hyperuricemic nephropathy occurs. Our recent studies have demonstrated that epidermal growth factor receptors is involved in the development of this disease in animals. Here we have made a summary on our findings and discussed related issues.

Keywords: Hyperuricemic nephropathy; Epidermal growth factor receptor; Tubulointerstitial fibrosis; Inflammation

Introduction

Hyperuricemic nephropathy

In recent years, as a result of improvements in diet and living standards, food intake has been rich in protein and purine, which is known to result in an increased incidence of hyperuricemia [1]. Hyperuricemia, which is defined by uric acid levels exceeding 7.0 mg/dL in men and 6.0 mg/dL in women [2] and is strongly associated with chronic kidney disease (CKD) [3]. Increasing evidence indicates that sustained uric acid is a risk factor that causes or exacerbates kidney fibrosis in the progression of CKD [4]. In our previous study, we found that raising uric acid levels in rats can induce glomerular hypertension and renal diseases as noted by the development of arteriosclerosis, glomerular injury and tubulointerstitial fibrosis [3]. In addition, the increased level of serum uric acid also tightly related to other diseases, such as hypertension, hyperlipidemia, atherosclerosis, coronary heart disease and diabetes [2,5-10].

Uric acid is the final metabolic product of purine metabolism in humans due to a lack of the enzyme uricase [11]. In other mammals, as a result of uricase located in the liver, uric acid can be broken down into allantoin. Thus, when considering the process of human evolution, a higher level of serum urate may confer a selection advantage due to the antioxidant effects of urate [12]. Blood levels of uric acid are tightly regulated by reabsorption and excretion mechanisms in the kidney. Excretion of uric acid in the kidney is carried out with the assistance of uric acid transporters. The transporters are divided into two categories: urate reabsorption transporters and urate excretion transporters [13].

Urate reabsorption transporters have three members: urate anion transporter 1 (URAT1), organic anion transporter 4 (OAT4) and glucose transporter 9 (GLUT9). Urate excretion transporters also include two categories: 75 the uptake of uric acid transporters and the excretion of uric acid transporters. To date, more than ten OAT species

have been identified [14]. OAT1 (SLC22A6) and OAT3 (SLC22A8) mainly assist the uptake of uric acid from blood to intracellular tubular cells. Increasing evidence has indicated that while the functions of these urate transporters are broke down, the level of uric acid in human body is increasing, resulting in hyperuricemia nephropathy (HN) [15-17].

Hyperuricemia has been considered as an independent risk factor in the progression of HN. Elevation of the serum uric acid level induces oxidative stress and endothelial dysfunction, resulting in the development of both systemic and glomerular hypertension combined with elevated renal vascular resistance and reduction of renal blood flow [18-20]. Hyperuricemia is also able to induce an epithelial to mesenchymal transition, which has direct effects on the tubular epithelial cell injury [21]. Moreover, numerous observations suggested that uric acid crystals are formed and deposited in the collecting duct of the nephron, infiltrated by monocytes/macrophages [22].

The role of EGFR in hyperuricemic nephropathy

Recently, we have indicated that blockage of epidermal growth factor receptor (EGFR) can attenuate the development of HN [4]. Numerous studies have demonstrated that the activation of TGF- β 1 signaling pathway is essential to glomerular sclerosis and tubulointerstitial fibrosis inducing by hyperuricemia [23-25]. TGF- β 1 contributes to fibrosis in two ways, one way is combining with TGF- β receptors and activating downstream Smad3. Then activated Smad3 in combination with Smad4, up regulated the expression of TGF- β 1-targeted genes in the nucleus [26]. The other is inducing fibrosis via activation of epidermal growth factor receptor (EGFR) independently [27,28].

EGFR is a member of receptor tyrosine kinases protein family, and activation of EGFR results in different cellular consequences that are related to fibrosis, including cell proliferation, migration, differentiation and transformation [29,30]. Moreover, numerous studies revealed that activation of EGFR is associated with the pathogenesis of renal interstitial fibrosis [31,32]. In our previous study, we observed the role of EGFR in chronic kidney disease in a rat model

of HN induced by oral administration of a mixture of adenine and potassium oxonate. We found that renal function was improved and glomerular sclerosis was attenuated as well as renal interstitial fibrosis after treatment of gefitinib, a special inhibitor of EGFR, in hyperuricemic rats. Activation of TGF- β signaling, increasing level of pro-inflammatory cytokines/chemokines and elevation of XOD activity induced by uric acid were also inhibited by EGFR blockage. Additionally, inactivation of EGFR preserved the level of OAT1 and OAT3. As numerous evidence has demonstrated that EGFR signaling activation is essential to the production of TGF- β 1 in mice models of renal fibrosis induced by unilateral ureteral obstruction (UUO) injury, we also suggested that blockage of EGFR decreased phosphorylation of Smad3 the level of TGF- β 1 in the rat model of HN [23,31]. Our results also showed that inhibition of EGFR suppressed phosphorylation of ERK1/2, which was activated by uric acid *in vivo* and *in vitro*. These data were accordance with Chen's report that EGFR contributed to expression of TGF- β 1 via ERK1/2 activation [33].

Summary

With all these data, we have displayed that inhibition of EGFR prevented the progression of hyperuricemia-induced nephropathy and preserved the function of kidney in a rat model. This renal protective effect occurs through inhibition of TGF- β signaling, suppression of inflammation and decreasing levels of uric acid via protecting expression of urate transporters. Therefore, EGFR may play a critical role in hyperuricemia nephropathy.

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