

Epidermal growth factor receptor signaling and the progression of diabetic nephropathy

Diabetic nephropathy is a life-threatening complication in patients with diabetes mellitus; it is the leading cause of end-stage renal disease worldwide, and is associated with higher cardiovascular morbidity and mortality. Although the intensive control of glucose and blood pressure by blocking the renin–angiotensin system has been shown to prevent the development and progression of diabetic nephropathy as well as cardiovascular events to some extent, the residual risk for the progression of diabetic nephropathy is still high¹. Thus, active investigations to understand the underlying mechanisms by which diabetes predisposes patients to the development and progression of diabetic nephropathy have implicated a variety of causal factors, such as altered intracellular signaling, the accumulation of advanced glycation end products and the overproduction of inflammatory cytokines^{2,3}. Of these, the crucial role of transforming growth factor (TGF)- β action in mediating progressive glomerulosclerosis and tubulointerstitial fibrosis has been intensively investigated⁴. We have recently reported that inhibiting dipeptidyl peptidase-4 (DPP-4) activity with the DPP-4 inhibitor, linagliptin, ameliorated diabetes-induced glomerulosclerosis and tubulointerstitial fibrosis through the inhibition of endothelial mesenchymal transition by blocking TGF- β 2/DPP-4/miR29s cross-talk in streptozotocin (STZ)-induced diabetic mice⁵. Recently, Chen *et al.*⁶ implicated the role of epidermal growth factor receptor (EGFR) phosphorylation in mediating TGF- β -induced renal fibrosis

and its inhibition by the EGFR inhibitor, erlotinib, in STZ-induced diabetic mice.

To extend their findings, Zang *et al.*⁷ reported that EGFR inhibition with erlotinib treatment slowed the progression of diabetic nephropathy in association with a decrease in endoplasmic reticulum (ER) stress and an increase in autophagy in STZ-induced diabetic endothelial nitric oxide synthase (eNOS) knockout mice. The findings here support the results of Zang *et al.*⁷ in that the EGFR inhibitor, erlotinib, clearly inhibited renal ER stress based on the expression of C/EBP homologous protein, protein kinase ribonucleic acid-like endoplasmic reticulum kinase and binding immunoglobulin protein, and enhanced autophagy based on the increased expression of autophagy-related protein 12, beclin and microtubule-associated protein light chain 3 AII and the decreased expression of sequestosome 1/p62 in the kidney of STZ-induced diabetic eNOS knockout mice. Because both enhanced ER stress and decreased autophagy are coordinately associated with the pathogenesis of diabetic nephropathy and because preventing these changes have recently been the focus as new therapeutic targets^{8,9}, the current findings by Zang *et al.*⁷ suggest a strong therapeutic potency of EGFR inhibition in diabetic nephropathy (Figure 1).

The upstream signaling regulation of autophagy is mainly by two intracellular nutrient-sensing kinases, adenosine monophosphate-activated protein kinase (AMPK) and mammalian target of rapamycin complex 1 (mTORC1). Autophagy is activated by the AMPK-mediated phosphorylation of UNC-51-like kinase 1 (ser317), and is suppressed by the mTORC1-mediated phosphorylation of UNC-51-like kinase 1 (ser757)¹⁰. Previous reports have shown that AMPK activity is decreased, whereas mTORC1

activity is increased in the kidneys of diabetic mice compared with non-diabetic mice^{11–14}, suggesting that both kinases might be involved in the upregulation of autophagy in erlotinib-treated STZ-induced diabetic eNOS^{-/-} mice. Indeed, Zang *et al.*⁷ showed that EGFR inhibition with erlotinib increased AMPK activity based on the increased phosphorylation of AMPK- α and AMPK- β , whereas it decreased mTORC1 activity based on the decreased phosphorylation of phosphorylated p70 ribosomal protein S6 kinase (p70S6K) and eukaryotic translation initiation factor 4B. Thus, they concluded that EGFR inhibition modifies the intracellular nutrient-sensing signals and subsequently activates autophagy, resulting in the amelioration of diabetic nephropathy. However, the detailed molecular mechanisms underlying the interaction between EGFR signaling and two nutrient-sensing signals remain unclear.

The cross-talk between mTORC1 and ER stress has recently highlighted their possible pathogenic roles in diabetic nephropathy. For instance, Inoki *et al.*¹³ reported that the interaction between mTORC1 and ER stress in glomerular podocytes plays a pivotal role in mediating the development and progression of diabetic nephropathy. Briefly, Inoki *et al.*¹³ found that binding immunoglobulin protein induced by ER stress was over-expressed, and its accumulation was significantly reduced by treatment with an mTORC1-specific inhibitor, rapamycin, in podocyte-specific mTORC1-activated mice, which suggested that the elevated ER stress is induced by mTORC1 activation. Interestingly, Zang *et al.*⁷ provided the first evidence that altered bidirectional interaction between ER stress and mTORC1 is involved not in only podocyte damage, but also in tubular epithelial cell damage in the progression of

*Corresponding author. Daisuke Koya

Tel: +81-76-286-2211

Fax: +81-76-286-6927

E-mail address: koya0516@kanazawa-med.ac.jp

Received 9 November 2014; revised 14 November

2014; accepted 16 November 2014

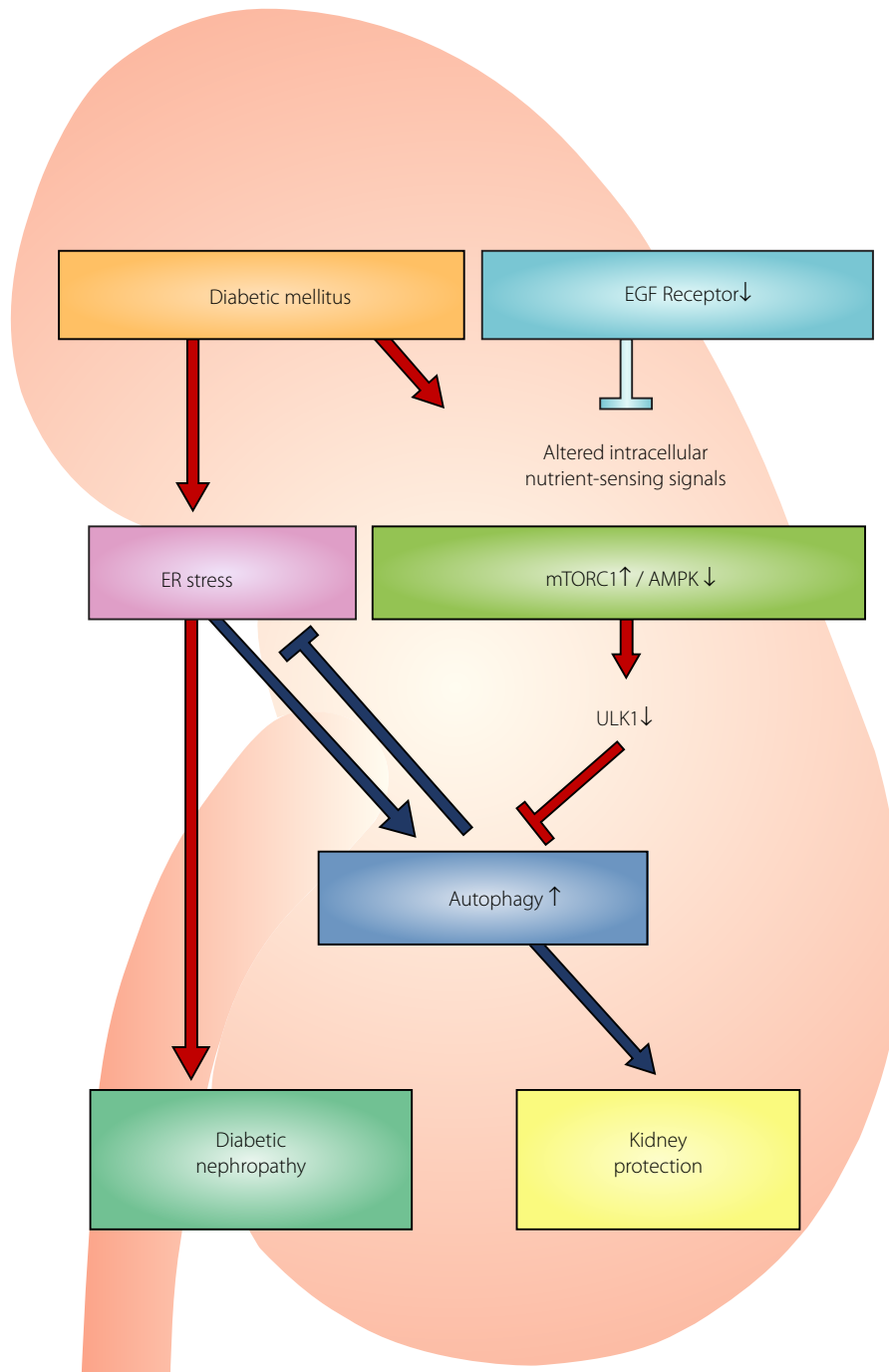


Figure 1 | Diabetes mellitus-related endoplasmic reticulum (ER) stress is a potent pathogenic factor of diabetic nephropathy. Healthy kidney cells have the ability to induce autophagy to overcome prolonged ER stress conditions, leading to kidney protection (blue lines and boxes). Autophagy is negatively and positively regulated by two intracellular nutrient signals, mammalian target of rapamycin complex 1 (mTORC1) and adenosine monophosphate-activated protein kinase (AMPK), respectively. Diabetes mellitus-related hypernutrient condition activates mTORC1 and suppresses AMPK, leading to autophagy inhibition through the inactivation of UNC-51-like kinase 1 (ULK1), a critical regulatory protein to initiate autophagy. Altered intracellular nutrient-sensing signal-mediated autophagy inhibition is involved in the progression of diabetic nephropathy via the enhancement of ER stress (red lines and boxes). Epidermal growth factor receptor (EGFR) inhibition slows the progression of diabetic nephropathy with a reduction in ER stress and an increase in autophagy by amelioration of altered nutrient-sensing signals (light blue line and box).

diabetic nephropathy. Collectively, the cross-talk between mTORC1 and ER stress could be involved in the pathogenesis of both podocyte and tubular cell damage in diabetic nephropathy, and might become a potential therapeutic target.

More recently, Chen *et al.*¹⁵ reported that podocyte-specific EGFR knockout mice were resistant to the progression of diabetes-related podocyte damage, although the relationship between EGFR signaling, nutrient-sensing signals and autophagy was not shown in the study. A recent study by Fang *et al.*¹⁶ showed that autophagy activity was suppressed in a mTORC1-dependent manner in podocytes of diabetic mice. Therefore, I am curious about how podocyte-specific EGFR gene deletion in mice affects diabetes-related hyperactivation of mTORC1 and the inhibition of autophagy in podocytes, which could provide further evidence that EGFR-mediated regulation of intracellular nutrient-sensing is involved in the pathogenesis of diabetic nephropathy.

In summary, the current understanding based on a series of EGFR research studies might shed light on a potential therapeutic implication of EGFR inhibition in diabetic nephropathy. Further studies are required of cross-talk between EGFR and intracellular nutrient-sensing signals.

DISCLOSURE

The author declares no conflict of interest.

Daisuke Koya*

Diabetology & Endocrinology, Kanazawa Medical University, Kahokugun, Ishikawa, Japan

REFERENCES

1. Koya D, Araki S, Haneda M. Therapeutic management of diabetic kidney disease. *J Diabetes Invest* 2011; 2: 248–254.
2. Koya D, King GL. Protein kinase C activation and the development of diabetic complications. *Diabetes* 1998; 47: 859–866.
3. Soldatos G, Cooper ME. Diabetic nephropathy: important pathophysiologic mechanisms. *Diabetes Res Clin Pract* 2008; 82 (Suppl 1): S75–S79.
4. Ziyadeh FN. Mediators of diabetic renal disease: the case for tgf-Beta as the major mediator. *J Am Soc Nephrol* 2004; 15 (Suppl 1): S55–S57.
5. Kanasaki K, Shi S, Kanasaki M, *et al.* Linagliptin-mediated DPP-4 inhibition ameliorates kidney fibrosis in streptozotocin-induced diabetic mice by inhibiting endothelial-to-mesenchymal transition in a therapeutic regimen. *Diabetes* 2014; 63: 2120–2131.
6. Chen J, Chen JK, Nagai K, *et al.* EGFR signaling promotes TGFbeta-dependent renal fibrosis. *J Am Soc Nephrol* 2012; 23: 215–224.
7. Zhang MZ, Wang Y, Paueksakon P, *et al.* Epidermal growth factor receptor inhibition slows progression of diabetic nephropathy in association with a decrease in endoplasmic reticulum stress and an increase in autophagy. *Diabetes* 2014; 63: 2063–2072.
8. Cunard R, Sharma K. The endoplasmic reticulum stress response and diabetic kidney disease. *Am J Physiol Renal Physiol* 2011; 300: F1054–F1061.
9. Kume S, Thomas MC, Koya D. Nutrient sensing, autophagy, and diabetic nephropathy. *Diabetes* 2012; 61: 23–29.
10. Kim J, Kundu M, Viollet B, *et al.* AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat Cell Biol* 2011; 13: 132–141.
11. Kume S, Uzu T, Araki S, *et al.* Role of altered renal lipid metabolism in the development of renal injury induced by a high-fat diet. *J Am Soc Nephrol* 2007; 18: 2715–2723.
12. Kitada M, Kume S, Imaizumi N, *et al.* Resveratrol improves oxidative stress and protects against diabetic nephropathy through normalization of Mn-SOD dysfunction in AMPK/SIRT1-independent pathway. *Diabetes* 2011; 60: 634–643.
13. Inoki K, Mori H, Wang J, *et al.* mTORC1 activation in podocytes is a critical step in the development of diabetic nephropathy in mice. *J Clin Invest* 2011; 121: 2181–2196.
14. Yamahara K, Kume S, Koya D, *et al.* Obesity-mediated autophagy insufficiency exacerbates proteinuria-induced tubulointerstitial lesions. *J Am Soc Nephrol* 2013; 24: 1769–1781.
15. Chen J, Chen JK, Harris RC. EGF Receptor deletion in podocytes attenuates diabetic nephropathy. *J Am Soc Nephrol* 2014. doi: 10.1681/ASN.2014020192.
16. Fang L, Zhou Y, Cao H, *et al.* Autophagy attenuates diabetic glomerular damage through protection of hyperglycemia-induced podocyte injury. *PLoS One* 2013; 8: e60546.

Doi: 10.1111/jdi.12317