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Microparticles as mediators of high glucose-induced toxicity in diabetic nephropathy

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Diabetic nephropathy (DN) is the most common cause of chronic kidney disease and end-stage renal disease worldwide. Sustained hyperglycemia or high glucose levels act as noxious stimuli and initiate several maladaptive signaling pathways such as endoplasmic reticulum (ER) stress, epithelial-mesenchymal transition (EMT) and mammalian target of rapamycin (mTOR), which are thought to play a major role in the etiology of DN. Nevertheless, the secondary mediators of hyperglycemia-induced renal injury are poorly understood. Microparticles (MPs), which are small vesicles containing bioactive signals shed by cells upon activation or during apoptosis, are elevated in diabetes and identified as biomarkers in DN. However, the role of MPs in the pathophysiology of DN remains unclear. In this study, we examined the effect of MPs shed from renal proximal tubular cells (RPTCs) exposed to high glucose conditions on naïve RPTCs *in vitro*. RPTCs exposed to high glucose-derived MPs showed increased levels of phosphorylated forms of eIF2α (an ER stress marker) and 4-EBP1 (a downstream target of mTOR). Moreover, a 1.3-fold increase in the expression of EMT marker α-SMA and a 1.6-fold increase in the levels of phosphorylated SMAD2 (a marker of transforming growth factor-beta signaling implicated in renal fibrosis) was observed in RPTCs treated with MPs. Together, our studies indicate that MPs do not alter the viability but induce ER stress and EMT and activate mTOR signaling in RPTCs. Thus, we conclude that MPs serve as mediators of pathologic cell signaling and contribute to fibrosis of RPTCs under high glucose conditions. Pharmacological interventions targeted to inhibit generation of MPs from renal cells might serve as an effective therapeutic strategy to prevent renal fibrosis and the progression of renal disease in patients with diabetes.