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Transglutaminase 2 regulates mesangial IgA1 deposition through RhoA-mediated vesicle-trafficking pathway in IgAN

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Objectives: IgA nephropathy (IgAN) is the commonest primary glomerulonephritis and characterized by mesangial deposition of IgA1. Although knockout of Transglutaminase 2 (TGase2) ameliorates mesangial IgA1 deposition and clinical symptoms in humanized mice model of IgAN, the pathway through which TGase2 is transferred to membrane and contributes to IgA1 deposition has not been elucidated.

Methods: We used mass spectrometry to identify protein partners of membrane TGase2 from *in vitro* cell model of mesangial deposition of polymetric IgA1 (pIgA1) isolated from IgAN patients, and utilized Gene Ontology and STRING database to analyze the pathway and protein interaction. The interactions of TGase2 and its partner with pIgA1 were analyzed by immunofluorescence, flow cytometry and Western blot.

Results: We found that TGase2 was expressed in the cytoplasm and on the membrane of human mesangial cells (HMC). More membrane TGase2 were expressed after pIgA1 depositing on HMC. Inhibition of TGase2 activity remarkably reduced the amount of pIgA1 binding to HMC. Mechanistically, we demonstrated 535 potential TGase2 binding proteins involved in exocytosis, vesicle tracking, cytoskeleton and actin dynamics, and other physiological activities, which were overlap observed for the membrane fraction with or without pIgA1 deposition. Inhibition of vesicle tracking pathway by Exo1 could reduce the amount of membrane TGase2 expression and pIgA1 binding to HMC. Additionally, STRING results revealed RhoA specifically interacted with membrane TGase2 after pIgA1 deposition. In the mesangial area of IgAN patients, RhoA immunostaining was increased and co-localized with TGase2 and IgA1. *In vitro*, membrane TGase2 was coprecipitated with RhoA of which expression was induced by pIgA1. Knockdown of RhoA greatly impaired membrane TGase2 expression that was upregulated by pIgA1 deposition. While overexpression of RhoA significantly increased membrane TGase2 expression, as well as pIgA1 deposition which could be decreased by TGase2 inhibition.

Conclusions: We demonstrate that TGase2 regulates mesangial IgA1 deposition through RhoA-mediated vesicle-trafficking pathway in IgAN.