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Kruppel like factor 15 is a crucial suppressor of the glomerular epithelial cell fibrosis in hypertension

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Objectives : Hypertension in glomerulus is known to be an initial stimulus for the fibrosis which results in the chronic kidney disease. We exerted a pressure by rotational force on glomerular epithelial cell to mimic hypertension environment. The effect of mechanical pressure on kidney fibrosis was evaluated and Kruppel like factor 15 (KLF15), which is an important modulator of fibrosis in chronic kidney disease, was assessed.

Methods : We proposed a method to induce the glomerular epithelial cell fibrosis by applying mechanical pressure through rotational force, which mimics in vivo environment of the glomerulus of a patient with hypertension (Figure). The device can generate different pressures by mitigating revolutions per minute (RPM). Human primary podocytes extracted from glomeruli were cultured under pressure using the device. 6-well plates with cells were placed on the dish support and rotated at different RPMs inside an incubator at 37°C in a humid 5% CO2 atmosphere. Levels of KLF15, WT-1 and fibronectin were measured through Western blotting and immunofluorescence at a range of RPMs

Results : The amount of pressure generated with rotational force was measured with a digital pressure sensor. The RPM was mitigated from 100 to 350, and we observed that the pressure level increases from 0.4 to 13.4 mmHg, respectively, as RPM increases. The human primary podocytes were cultured at static, 4 mmHg and 8 mmHg condition for 3 hours. Expression of fibronectin significantly increased as the pressure level increased, which indicates that fibrosis is formed. The level of fibrosis induction was comparable to that of TGFβ. Moreover, we observed that increasing pressure level suppressed expression of WT-1 and KLF15. These results indicated a negative correlation between the level of KLF15 and the abundance of fibronectin. Lastly, we also observed an effect of pressure at 4mmHg for 48 hours, and found statistically

significant changes in the levels of fibronectin, WT-1, KLF15, podocalyxin and synaptopodin through real time PCR. Expression of fibronectin increased, and expressions of WT-1, podocalyxin, and synaptopodin decreased when the podocytes were cultured under pressure.

Conclusions : We generated glomerular epithelial cell fibrosis by mechanical pressure stimulation through the proposed device. The molecular analysis of stimulated podocytes has shown that KLF15 plays a crucial role in kidney fibrosis inhibition. This mechanism may be applied as a potential therapeutic target in hypertension-associated kidney fibrosis.

Keywords : podocyte; KLF15; fibrosis; rotational force