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A noninvasive mouse model of chronic kidney disease induced by podocyte-specific overexpression of human transforming growth factor-β1

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Chronic kidney disease (CKD) is a common complication of several diseases including diabetes mellitus, hypertension and chronic glomerulonephritis. Approximately 10% of adults in developed countries suffer from CKD. Clinical progression of CKD leads to end-stage kidney disease (ESKD) that can be treated only with renal replacement therapy including dialysis and renal transplantation. Especially, diabetic nephropathy is the leading cause of ESKD and the cause of a half of new dialysis cases. There is currently no other therapeutic option for ESKD patients. The main reason of the scarce therapeutic strategies for this chronic and fatal disease is the lack of useful disease model to evaluate drug discovery. In the present study, we focused on the potent profibrotic activity of transforming growth factor-β1(TGF-β1) and its critical mechanistic role in glomerulosclerosis. We prepared and amplified a chimeric mouse podocin/human TGF-β1 bacterial artificial chromosome construct, purified, linearized, separated by pulsed field gel electrophoresis and dialyzed before microinjection into fertilized eggs. We obtained several founders expressing the transgene as demonstrated by Southern blotting. As expected, the plasma levels of human TGF-β1, creatinine and blood urea nitrogen were elevated in the transgenic mice from 8-weeks of age. The urine levels of fatty acid-binding protein, a marker of kidney injury, and human TGF-β1 were also significantly higher in the transgenic mice compared to wild type mice. Trichrome staining of the kidneys disclosed extensive deposition of extracellular matrix proteins in the transgenic mice compared to their wild type counterparts. Moreover, mRNA levels of several fibrotic markers were significantly increased in human primary podocyte cells treated with human TGF-β1. In addition to highlighting the important role of TGF-β1 in the pathogenesis of kidney fibrosis, this investigation made possible the development of a novel mouse model of kidney fibrosis that may be useful for drug discovery.

Biography

Atsuro Takeshita(MD) was graduated from Mie University (Mie, Japan) in 2011. He was trained as a junior resident in Saiseikai Matsusaka General Hospital (Mie, Japan, 2011-2013). After working as a junior resident, he is working as a physician of diabetes and endocrinology department at Mie University Hospital (Mie, Japan, 2013-), and Ise Red Cross Hospital (Mie, Japan, 2014-2015). He also entered the Department of Diabetes and Endocrinology, Mie University Graduates School of Medicine in 2015. From 2018, he is an assistant Professor at the Department of Immunology in Mie University School of Medicine and he is studying to find the novel treatment of chronic kidney disease using several animal models.

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