【Award Session-1】

Targeting angiopoietin-2 in kidney fibrosis: focus on inflammation and endothelial activation

抑制第二型血管生成素可透過血管內皮細胞改善發炎反應及腎臟纖維化

Fan-Chi Chang

張芳綺

Clinical Associate Professor of the Department of Internal Medicine in National Taiwan University College of Medicine

臺大醫院 腎臟科

We have conducted extensive research into the pathogenic role of dysregulated angiopoietin/Tie-2 system in chronic kidney disease (CKD) and CKD-related cardiovascular disease. The angiopoietin/Tie-2 signaling is crucial in controlling vascular stability during angiogenesis. Constitutive activation of Tie-2 induced by Angpt1 is fundamental in maintaining vascular quiescence, endothelial survival, and acts as an anti-inflammatory signal. Angiopoietin-2, generally considered as an antagonist of Tie-2, leads to endothelial apoptosis and vascular regression by destabilizing endothelial cells and priming them to respond to exogenous stimuli such as tumor necrosis factor-α and vascular endothelial growth factor.

Our studies has revealed that plasma levels of angiopoietin-2 are increased in patients with CKD, and are associated with albuminuria, microinflammation (PLoS One, 2013;8(3)e54668), and metabolic syndrome (JFMA 2021; 23:S0929-6646(21)00188-1). Furthermore, murine models of CKD demonstrate an increase in angiopoietin-2 in both plasma and kidney, which leads to increased expression of collagen and pro-fibrotic genes in aortic vascular smooth muscle cells. Angiopoietin-2 stimulates endothelial expression of chemokines and adhesion molecules and increases Ly6Clow macrophages in the aorta (JASN 2014;25(6):1198-209).

Our team has focused on the role of dysregulated angiopoietins in CKD progression. In a cohort of 319 patients with CKD, both plasma angiopoietin-2 and angiopoietin-2/angiopoietin-1 ratios were positively associated with the occurrence of end-stage kidney disease. In mice with progressive kidney disease induced by either ureteral obstruction or ischemia-reperfusion injury, overexpression of human angiopoietin-1 in the kidney tubules with Pax8-rtTATg;pTRE-hAngpt1Tg transgenic mice not only reduced macrophage infiltration in the initial stage post-injury but also attenuated endothelial cell apoptosis, microvascular rarefaction, and kidney fibrosis in the advanced disease stage. Notably, angiopoietin-1 attenuated chemokine C-C motif ligand 2 (CCL2) expression in the endothelial cells of the fibrosing kidneys, and these protective effects led to attenuation of functional impairment. Mechanistically, angiopoietin-1 reduced CCL2-activated macrophage migration and protected endothelial cells against cell apoptosis induced by angiopoietin-2 and Wnt ligands. We applied L1-10, an angiopoietin-2 inhibitor, to murine models of progressive kidney disease and found inhibitory effects on macrophage infiltration, microvascular rarefaction, and kidney fibrosis. Our research

highlights the detrimental impact of increased angiopoietin-2 on kidney survival in patients with CKD, manifested by angiopoietin-2 induced endothelial CCL2-activated macrophage infiltration and endothelial cell apoptosis in their kidneys undergoing fibrosis.

We are confident that angiopoietin-2 plays a crucial role in endothelial activation, inflammation, and endothelial apoptosis in CKD. CKD has caused tremendous socioeconomic burden to the country. Inflammation and capillary rarefaction are the cardinal and interconnected features in kidney fibrosis, which is the ultimate consequence of kidney failure. We believe that our research into targeting renal endothelium through inflammatory and angiogenic pathway will contribute to the development of encouraging therapeutic targets.