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Cardiac cysteine and glycine rich protein 3 (CSRP3) induces renal myogenesis leading to CKD

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Keywords

Cardiorenal syndrome type 1, Acute kidney injury, Chronic kidney disease, fibrosis, hypertension

Abstract

Introduction: Acute cardiac injury with renal injury (acute cardiorenal syndrome) can induce chronic kidney disease (CKD), but mechanisms by which heart injury signals to kidney are unclear. Cardiac LIM protein (CSRP3) is a cardiomyocyte differentiation factor which is released into plasma after cardiac arrest. We hypothesized that CSRP3 induces myogenesis in the renal proximal tubule, inducing CKD.

Methods: Two kidney injury models which result in similar acute kidney injury were tested, renal ischemia-reperfusion injury (IRI) or cardiac arrest and cardiopulmonary resuscitation (CA/CPR). Seven weeks later, blood pressure (BP) and glomerular filtration rate (GFR; µg/min/100g) were measured, then mice were sacrificed. Single nucleus RNA sequencing (snRNAseq) was conducted on mouse kidney cells harvested 24h after CA/CPR. Primary human proximal tubular epithelial cells (hPTEC) were cultured from research-designated human kidneys. Recombinant CSRP3 (rCSRP3) was administered to hPTEC followed by RNAseq. Lastly, mice were injected with rCSRP3 after IRI, then sacrificed 7 weeks later.

Results: CA/CPR (n=8) induced worse CKD than IRI (n=8) despite identical 24h GFR: GFR (CACPR 732.3+31.03 vs IRI 933.3+52.55, $p<0.01$); fibrosis (VaSMA/Vkid; CA/CPR 1.05±0.086 vs IRI 0.68±0.068, $p<0.05$); albuminuria (CACPR 0.032±0.005 mg vs IRI 0.132±0.026 mg, $p<0.01$). Compared with IRI, CA/CPR caused renovascular hypertrophy (thickness index; CACPR 0.75±0.038 vs IRI 0.49±0.011, $p<0.01$) and hypertension (BP ratio: CACPR 1.22±0.029 vs IRI 0.98±0.069, $p<0.01$). SnRNAseq demonstrated that CA/CPR upregulated muscle cell differentiation ontologies in proximal tubule cells, driven by regulation of 110/162 myogenesis genes. In hPTEC, CSRP3 induced myogenesis differentiation factor 1 (MyoD1)>30 fold. CSRP3 injection in IRI mice resulted in lower GFR (CSRP3(+) 785.5±34.16 vs CSRP3(-) 954.2±55.69, $p<0.05$), and more renovascular hypertrophy (CSRP3(+) 0.61±0.011 vs CSRP3(-) 0.51±0.011, $p<0.01$, n=8/group) compared with IRI without CSRP3.

Conclusions: CA/CPR caused CKD, renovascular hypertrophy, and hypertension associated with tubular myogenesis. CSRP3 induced myogenesis pathway in hPTEC and in mice. CSRP3 may drive cardiorenal-induced CKD.se the OHSU Body Text style for the body text of your abstract.