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Promoting Sustainable Kidney Health: The Asia-Pacific and Beyond

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Small extracellular vesicles derived from damaged muscle aggravate the progression of kidney fibrosis

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Objectives : The prevalence of chronic kidney disease (CKD) has been increasing. Sarcopenia is often associated with increased morbidity and mortality of CKD patients, whereas exercise- and genetic engineering-induced muscle hypertrophy is reported to attenuate the progression of CKD. Since muscle-derived extracellular vesicles (EVs) contribute to muscle-organ crosstalk, the present study examined whether EVs from damaged muscle mediate the progression of kidney injury.
Methods : Unilateral ureteral obstruction (UUO) was performed in the tibial nerve denervation-induced muscle atrophy mice (denervation + UUO). Muscle cell injury was induced in C2C12 cells by dexamethasone or TGFβ1. EVs from mouse plasma and conditioned media were isolated using a commercial kit. To confirm the delivery of EVs to the injured kidney, PHK67-labeled plasma EVs were intravenously administrated to UUO mice and mProx24 cells were pre-treated with isolated EVs followed by TGFβ1 treatment.
Results : As a result, denervation decreased muscle strength as well as mass and increased expression of atrogenes and mitochondrial dysfunction. UUO-induced kidney inflammation and fibrosis were aggravated in the denervated mice. Markers of EV were increased in the plasma as well as damaged muscle in the denervated mice. Interestingly, PHK67-labeled EVs were accumulated in the obstructed kidneys. EVs isolated from the denervated mice and conditioned media from damaged C2C12 cells aggravated TGFβ-induced upregulation of fibrotic genes in mProx24 cells. Additionally, inhibition of EVs synthesis/secretion by GW4869 partly reversed kidney inflammation and fibrosis in denervation + UUO mice.
Conclusions : In conclusion, the present data showed the pathogenic role of EVs from damaged muscle in kidney injury of denervation + UUO mice as well as TGFβ1-induced mProx24 cell injury, suggesting that damaged muscle-released EVs may mediate kidney injury.