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Xiaonan Wang

Emory University, USA

Zhongda Hospital, Southeast University, China

Muscle-derived miR-26a mediate cardiac fibrosis through exosomes in chronic kidney disease mice

Uremic cardiomyopathy and muscle atrophy contribute to CKD-induced morbidity and mortality. Exosomes, natural carriers of many signal molecules including microRNA (miR), mediate organ-to-organ communication. We hypothesized that miR-26 would benefit both CKD-induced muscle wasting and cardiomyopathy through exosome-mediated muscle-heart crosstalk. We used an engineered exosome vector, which contains an exosomal membrane protein gene Lamp2b fused with muscle specific surface peptide for targeting delivery. Exosome encapsulated miR-26a precursor RNA (Exo/miR26) were injected into the tibialis anterior (TA) muscle of CKD mice (5/6 subtotal nephrectomy) for 10 weeks. miR-26a was decreased in skeletal muscle and heart of CKD mice. Uremic serum enhanced secretion of miR-26a exosomes in cultured C2C12 skeletal and H9C2 cardiac muscle cells. The intervention of Exo/miR26a increased the expression of miR-26a in skeletal muscle and heart, as well as increased muscle cross-section area and decreased CKD-induced up-regulation of atrogin-1 and MuRF1. Curiously, cardiac fibrosis lesion was partially depressed, and FoxO1, α-SMA, connect tissue growth factor (CTGF), fibronectin and collagen1α were decreased in CKD mice with intramuscular injection of Exo/miR-26a. Echocardiography showed that the percentage of ejection fraction was increased in CKD mice treated with Exo/miR26a. Using fluorescence dye labeled Exo/miR26a; we found that the fluorescence intensity in heart was correlated with skeletal muscle, examined by linear regression. We found that miR-26a directly inhibits FoxO1 and CTGF, which provided mechanism for inhibition of muscle atrophy and cardiac fibrosis by Exo/miR26a. Overexpression of miR-26a in muscle prevents CKD-induced muscle loss and attenuates cardiac fibrosis via exosome-mediated muscle-heart crosstalk.

Biography

Xiaonan Wang gained his MD in 1982 from Peking Union Medical College, Beijing, China. She finished her post-doc training in 1991 in the University of Colorado HSC, Denver, CO and in 1997 in Emory University, Atlanta, GA, USA. Currently, Wang is an Assistant Professor of Renal Division, Department of medicine. She has published 50 papers in peer review journal. Since 1997, Wang has focused on investigation of the molecular/cellular mechanisms that lead to protein malnutrition in, diabetes, chronic kidney disease and aging in order to develop therapeutic strategies for treatment. Wang uses transgenic mice, virus (adenovirus, adeno-associated virus (AAV) and lentivirus) mediated gene transfer and cell culture systems to test her hypotheses.

xwang03@emory.edu

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