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EDITORIAL COMMENT

Paracrine Factors in Uremic Cardiomyopathy*

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Uremic cardiomyopathy (UCM) is a severe complication in patients with chronic kidney disease (1,2). In these patients, cardiovascular complications account for approximately 50% of deaths. Clinically, UCM is characterized by severe uremia accompanied by systolic dysfunction, cardiomegaly, and pericarditis. These patients develop pathological cardiac remodeling, including hypertrophy, fibrosis, and inflammation. UCM is often the result of pressure and volume overload, in addition to the uremic state of the patients. Although dialysis improves UCM, the most beneficial treatment is kidney transplantation. Left ventricular hypertrophy (LVH) has been considered the primary manifestation of UCM. LVH is often the result of stretching of the extracellular matrix and the release of ligands known to contribute to the hypertrophic process, which occurs in response to pressure and volume overload. However, recent studies suggest that diastolic dysfunction associated with oxidative stress is the main cause of the detrimental effects of UCM.

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In this issue of *JACC: Basic to Translational Science*, Wang et al. (3) have shown that miR-155, which is present in exosomes derived from macrophages, regulates cardiomyocyte pyroptosis in UCM. Exosomes are small membrane vesicles ranging in size from 40 to 100 nm that are present in all tested body fluids; they carry nucleic acids, proteins, and lipids (4). Exosomes are an important vehicle for cellular and organ communication, and several studies have shown that exosomes released from a particular organ can affect gene expression remotely through delivery of their cargos to other organs. The best studied exosome cargos are microRNAs (miRs; miRNAs). miRs are small, approximately 22 nucleotide RNA molecules that regulate gene expression by targeting the 3′ untranslated region (UTR) of mRNAs, which results in translation suppression or RNA degradation. Several studies have shown that miRNAs contribute to cancer metastasis, cardiac hypertrophy, and renal diseases (5).

In this study, the investigators used a mouse model of UCM that consisted of a 2-step nephrectomy followed by salt supplementation; the study showed that pyroptosis was involved in the UCM response. Pyroptosis is a mechanism of programed cell death that is dependent on caspase 1 activation. Pyroptosis is also associated with inflammation. In the current study, the investigators have shown that in response to uremic conditions, macrophage-derived exosomes enhanced pyroptosis in the heart. The investigators have further shown that miR-155 was present in these exosomes and targeted expression of the Forkhead Transcription Factor 3a (FoxO3a). The investigators proposed an alternative cause of UCM that would be mostly due to increased inflammation and cell death. Although inflammation has been shown to be involved in UCM, this was the first report to address the contribution of pyroptosis to UCM.

In addition to dialysis and kidney transplantation, treatment for UCM has focused on drugs that target the renin-angiotensin system. Targeting this system is believed to improve UCM by reducing hypertrophy

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and fibrosis. The current work highlighted the importance of targeting inflammation and cell death, in addition to hypertrophy and fibrosis. The study thoroughly evaluated the consequences of UCM on cardiac function, fibrosis, and hypertrophy. Furthermore, the investigators examined if inhibition of miR-155 and over-expression of FoxO3a prevented the pathological effects of UCM. Moreover, the role macrophage-derived exosomes play in the pathological response to UCM was investigated in vivo through inhibition of exosome release and in vitro by treating primary cardiomyocytes with macrophage-derived exosomes. The investigators have conclusively and elegantly shown that pyroptosis is involved in UCM, and that exosomal macrophage-derived miR-155 targeting FoxO3a is a major player on cardiac dysfunction, cell death, fibrosis, and hypertrophy. However, further studies are necessary to investigate the role of exosomes and miRs on oxidative stress. Furthermore, the effect of macrophage-derived exosomes was only tested in cardiomyocytes; its effect on other cardiac cells needs to be investigated. Lastly, it is unclear if the observed cardiac dysfunction was a consequence of cell death, inflammation, and fibrosis, or if there were direct effects on sarcomeric proteins. To address these questions, it will be important to evaluate myocyte and myofibril function from the hearts of the various animal models used in this study.

Exosomes have been considered as a possible treatment option for several diseases (6). Engineered exosomes could potentially deliver cargos to targeted organs. However, it is still unclear what factors promote organ-specific delivery. As the field advances, it is possible to envision an effective treatment approach for UCM that would specifically deliver a miR-155 inhibitor to the heart, resulting in improved outcomes for this devastating disease.

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