Endothelial-to-Mesenchymal Transition and MicroRNA-21
The Game Is On Again

Elena Cavarretta, Michael V.G. Latronico, Gianluigi Condorelli

In the presence of any left ventricular dysfunction, be it systolic or diastolic, there is an increased risk of developing heart failure (HF). Survival expectancy has been improved in HF patients with reduced systolic function, but not for those with a normal ejection fraction.1,2 Moderate or severe diastolic dysfunction, which is predictive of all-cause death, has a prevalence of 7% in asymptomatic individuals and 75% among symptomatic HF patients.3 Regardless of its high prevalence, diastolic HF has received less attention than the systolic type.2

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The morpho-pathological correlate of diastolic dysfunction is reduced myocardial compliance due to cardiac fibrosis, whereby normal myocardial architecture is disrupted by excessive and disordered deposition of extracellular matrix and collagen.4 Myofibroblasts, the main players in this fibrotic process, can be derived from expansion and activation of resident tissue fibroblasts, from migration of bone marrow-derived circulating fibrocytes, and from endothelial-to-mesenchymal transition (EndoMT).5

Similar to epithelial-to-mesenchymal transition, endothelial-to-mesenchymal transition is a complex phenomenon in which endothelial cells acquire a mesenchymal phenotype, expressing mesenchymal markers, such as α-smooth muscle actin and type I collagen, instead of vascular endothelial cadherin. In the embryo, endothelial-to-mesenchymal transition is necessary for normal valvular and septal morphogenesis: In fact, the formation of the atrio-ventricular endocardial cushion is dependent on the differentiation of endothelial cells into mesenchymal cells that invade the cardiac jelly.6

The principal inducer of this process is transforming growth factor (TGF)-β, a multifunctional growth factor that signals via a classical pathway after binding to TGF-β type 2 receptor, activating TGF-β type 1 receptor and Smad-mediated transcriptional events (in particular those of Smad 2/3), but also via a Smad-independent signaling pathway, with the direct involvement of TGF-β–activated kinase 1.7 TGF-β also up- and downregulates the expression of numerous microRNAs, many of which have been extensively investigated.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Kumarswamy et al8 show in vitro and in vivo that microRNA-21 (miR-21) is involved in TGF-β–induced endothelial-to-mesenchymal transition via a PTEN/Akt-dependent pathway. miR-21, which has been implicated in human tumorigenesis and progression, is upregulated by TGF-β. In the endothelium, this growth factor increases expression of both primary and mature miR-21: after exposure to TGF-β, mature miR-21 expression is much higher in comparison with the primary transcript, an effect probably related to enhanced Smad-mediated processing of the primary precursor of miR-21.

The first report of a role for miR-21 in cardiac pathology was conducted on a murine model of pressure-overload–induced HF: Thum et al9 showed that miR-21 is a critical regulator of extracellular signal-regulated kinase/mitogen-activated protein kinase activity in cardiac fibroblasts, enhancing fibrosis by via inhibition of Sprouty 1. Regarding other organs, Zhong et al10 demonstrated that Smad3 signaling increases expression of miR-21 in the kidney to promote renal fibrosis in response to TGF-β1. Interestingly, Smad2 and Smad3 differentially regulated the post-transcriptional modifications of miR-21, Smad2 being a negative regulating factor for miR-21. TGF-β1 was also shown to be central mediator of fibrosis in the lung and, therefore, the induction of miR-21 by TGF-β1 may represent a potential therapeutic target.11 Liu et al12 showed that in mice treated with bleomycin, an inducer of pulmonary fibrosis, enhanced miR-21 expression was primarily localized to α-smooth muscle actin+ fibroblasts; a concomitant decrease in the expression of Smad7, a negative regulator of lung fibrosis, contributed to the profibrogenesis mechanism of miR-21.

The above results, obtained in different organs—heart, lung, and kidney9,10,12—concur in attributing miR-21 a pathological role in fibrosis. Moreover, knockdown of miR-21 was reported to significantly reduce the number of α-smooth muscle actin+ interstitial myofibroblasts and lessen interstitial collagen type I and fibronectin, hence, blunting renal fibrosis.10 Therefore, this microRNA may be a promising target for the therapy of fibrotic diseases.

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References
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