Left ventricular hypertrophy is an initial compensatory mechanism in response to cardiac stress that can degenerate into heart failure and sudden cardiac death. Recent studies have shown that microRNAs (miRs) regulate several aspects of cardiovascular diseases. In this issue of the *JCI*, Bang and colleagues identified an exosome-mediated communication mechanism between cardiac fibroblasts and cardiomyocytes. Specifically, cardiac fibroblasts secrete miR-enriched exosomes, which are subsequently taken up by cardiomyocytes, in which they alter gene expression. In particular, a passenger strand miR, miR-21*, was identified as a potent paracrine factor that induces cardiomyocyte hypertrophy when shuttled through exosomes. These advanced comprehensive analyses represent a major step forward in our understanding of cardiovascular physiopathology, providing a promising adjunctive target for possible therapeutic approaches, namely the miR-mediated paracrine signaling network.
Stargazing microRNA maps a new miR-21 star for cardiac hypertrophy

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The role of exosomes in LVH

Exosomes are a specific subset of secreted membrane vesicles that are relatively homogeneous in size (30–100 nm) and differ from apoptotic bodies and microvesicles in their density and specific protein and nucleic acid composition. Multiple cell types secrete exosomes through fusion of multivesicular bodies with the plasma membrane. Recently, cell-to-cell exosome-dependent transfer of selected miRs from endothelial cells to vascular smooth muscle was reported within the vessel wall (19). Moreover, a similar mechanism was described to mediate the transfer of AGO/miR complexes from platelets to endothelial cells (20).

In this issue of the JCI, Bang and coworkers report a miR-containing exosome-mediated intercellular communication system that operates within the myocardium. The data provided by Bang and colleagues support previous observations of miR-containing exosomes mediating responses in other cell populations and confirm miR-mediated intercellular communication in cardiac tissue (21). In particular, Bang and colleagues revealed that miR-21*, a passenger strand microRNA that is usually degraded inside the cytoplasm, is specifically packaged into and shuttled by exosomes from cardiac fibroblasts to cardiomyocytes, in which it promotes a hypertrophic response (Figure 1 and ref. 21). Interestingly, Bang et al. demonstrated that fibroblast-derived exosomes are selectively enriched with miR-21* and exosome uptake by cardiomyocytes was dependent on temperature and actin. Once released within cardiomyocytes, exosome-derived miR-21* led to a substantial increase in cardiomyocyte cell size (Figure 1).

Using proteomic profiling, Bang and colleagues identified sarcoplasmic protein sorbin and SH3 domain-containing protein 2 (SORBS2) and PDZ and LIM domain 5 (PDLIM5) as targets of miR-21* in cardiomyocytes, since both the encoding genes were strongly silenced in miR-21*-transfected cardiomyocytes. Of note, in the same cardiomyocyte model, knock down of SORBS2 and PDLIM5 resulted in marked cellular hypertrophy. SORBS2 localizes to Z-disks, in which it influences the contractile and elastic properties of cardiac sarcomeres (22). Interestingly, release of SORBS2 from damaged cardiac tissue into the bloodstream upon fatal acute myocardial infarction has been described recently (23). PDLIM5 is highly conserved across species and, like SORBS2, colocalizes at Z-disks and is directly associated with dilated cardiomyopathy (24) and indirectly involved in human hypertrophic cardiomyopathy (25). Collectively, these findings raise the question of whether miR-21* plays a role in the development of HF in Z-disk disruption models.

The study by Bang and colleagues has also provided new insights for LVH. In fact, miR-21* was detected in pericardial fluid of mice with transverse aortic constriction–induced cardiac hypertrophy (21), thus confirming in vivo that miR-21* plays an important role in regulation of the cardiac fibroblast secretome and in determining a hypertrophic response (Figure 1). In addition, Bang and associates were able to demonstrate that systemic injection of 80 mg/kg of a miR-21* antagomir at day 0 and day 2 prevented LVH induction by angiotensin II administration.

Future implications

The most intriguing aspect of the study performed by Bang and coworkers is the identification of a unique mechanism in which cardiac fibroblasts influence the hypertrophic response of cardiomyocytes (21). If confirmed by further studies, these findings provide a potential therapeutic target to interfere with cardiovascular diseases at a physiopathological level. Although fibroblast-derived miR-21* promotes an undesirable pathologic hypertrophy of cardiomyocytes, the identification of the exosome-dependent miR secretion mechanism has been addressed extensively. These vesicles and their miR cargo will likely represent an exciting therapeutic venue in the years to come for cardiovascular biology.

Many questions that pertain to the selective delivery of vesicle content to target cells, exosomes clearance in biologic fluids, and the possibility of a ligand-receptor interaction of surface membranes remain to be answered. The next steps in this field of research will be to further evaluate how miR-containing vesicles promote disease. Moreover, adjunctive efforts are needed to investigate miR-21* inhibition under pressure overload conditions on left ventricular function and survival. Finally, while the clinical use of antagonists for human
therapeutics looks to be part of future strategies for treating a variety of diseases (for example, miravirsen, a miR-122 antagonist, is currently being evaluated in a phase IIb trial for the treatment of virus C–related hepatitis; ref. 26), it remains unclear whether exosomes/microparticles can be exploited for selectively targeting and delivering biological therapies based on the modulation of miR effects.

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