Commentary: Why bother? The case for understanding interstitial cells in the aortic valve

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Central Message

Understanding osteogenic differentiation in aortic valve interstitial cells may enable preventive treatments that delay or slow calcification.

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Our usual tools, the stethoscope and echocardiogram, detect aortic valvular changes only after irreversible calcification. Aortic stenosis is, after all, the culmination of an indolent, decades-long disease process. When calcification leads to symptomatic stenosis, we have excellent surgical and interventional therapies. Why study this process? If we do find a way to intervene early, would we really offer a medical treatment to patients for whom aortic valve replacement is both remote and improbable? Truthfully, we cannot know until we look hard and deep at the disease mechanism.

In this issue of the *Journal*, Wang and colleagues¹ identify a positive feedback loop that promotes osteogenic differentiation of human aortic valve interstitial cells (hVICs). This differentiation is a prerequisite to valvular calcification and thus represents a critical turning point in the fate of the valve. They provide strong evidence that human antigen R (HuR)—an RNA-binding protein involved in myriad cellular pathways—drives osteogenic differentiation of hVICs. It does this in concert with the long noncoding RNA (lncRNA) MALAT1. HuR stabilizes MALAT1 which, in turn, sponges the microRNA mir191-3p, decreasing its effective local concentration. Mir191-3p normally acts to prevent transcription of HuR. When this microRNA is bound by MALAT1, there is increased transcription of HuR, further driving osteogenic differentiation. Essentially, HuR takes the brakes off its own transcription with the help of MALAT1, and osteogenesis ensues.

MALAT1 is one of several lncRNAs² and microRNAs^{3,4} recently implicated in hVIC osteogenic differentiation. These noncoding RNAs are responsible for posttranscriptional regulation—one control level of many in a sea of inflammatory processes.⁵⁻⁷ MALAT1 stands out as one of the few regulators with the signal amplification power of a positive feedback loop. Should this make MALAT1 a focal point in our search for a therapeutic window? HuR and MALAT1 are both ubiquitous transcriptional regulators. As such, they cannot be targeted

by medical therapy without prohibitive side effects. This positive feedback loop, however, cannot be ignored. Is there a way to prevent HuR activation in hVICs? Can this positive feedback loop be interrupted in hVICs without systemic changes to HuR and MALAT1? These are now vital questions that merit further investigation.

In our increasingly technology-driven world, auscultation is still the mainstay of first line screening for valve disease.⁸ In 2015, however, researchers from Massachusetts General reported that fluorodeoxyglucose positron emission tomography can identify precalcific inflammatory changes in aortic valves.⁹ Simply put, we no longer need to wait for a stethoscope to identify a problem that is decades in the making. And now that we can actually visualize the beginnings of aortic valve pathology, our need to understand the fundamental disease process is more pertinent than ever before. Preventive therapy for aortic valve disease is still a long way away, but it is getting closer all the time.

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