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Commentary: Harnessing the regenerative potential of the human heart

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Heart failure is a global epidemic, with an estimated prevalence of >37.7 million individuals worldwide.² Although advances in primary prevention and treatment of heart failure have improved outcomes, there remains an unmet need for therapies that could restore cardiac function by replenishing heart muscle cells that are lost or damaged in the setting of heart failure. In recent years, regenerative medicine has emerged as a promising avenue to develop such therapies. Broadly speaking, efforts in the field of cardiovascular regenerative medicine can be categorized into 2 approaches. The first consists in the lineage-specific differentiation of human pluripotent stem cells (hPSCs) to generate cardiomyocytes for transplantation. The second consists in unlocking the endogenous regenerative potential of the human heart through “cardiac rejuvenation.”

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Regeneration of the neonatal mouse myocardium following apical resection.¹

CENTRAL MESSAGE

Understanding the hormonal mechanisms that control cardiac regenerative capacity is essential to develop cardiac rejuvenation and stem-cell based therapies.

Support for this second approach was bolstered by the seminal work of Sadek and Porrello,¹ who demonstrated that during the neonatal period, the mammalian heart retains significant regenerative capacity but that this potential is lost shortly after birth (Figure 1). Proponents of the cell-free “cardiac rejuvenation” approach propose to use small molecules, recombinant proteins, or gene therapies to reprogram mature cardiomyocytes back to their “immature” state to restore their proliferative potential. Such a strategy requires a thorough understanding of the biological mechanisms underpinning human cardiac regeneration.

In this issue of the *Journal*, Sadek and Porrello³ discuss recent evidence on the role of thyroid hormone signaling in modulating the regenerative capacity of the heart. Their article focuses on a recently published study by Hirose

and colleagues,⁴ which demonstrated an inverse correlation between cardiac regenerative potential and thyroid hormone levels. Hirose and colleagues further introduced a novel evolutionary paradigm whereby the loss of cardiac regenerative potential is ontogenetically and phylogenetically associated with thyroid hormone-dependent acquisition of endothermy, thereby highlighting the evolutionary advantage of shutting down regenerative capacity after birth.

While Sadek and Porrello highlight the relevance of these findings to the field of “cardiac rejuvenation,” the authors also point out some important limitations that cast a doubt on the viability of thyroid hormone signaling as a therapeutic target for cardiac regeneration. The most important of these limitations is the fact that despite promising proof-of-concept studies in model organisms, there is currently no convincing evidence demonstrating that acute modulation of thyroid hormone signaling in humans can promote cardiac regeneration following injury. Furthermore, the interplay of thyroid hormone signaling with other triggers of cardiac maturation—such as a highly oxidative metabolic environment^{5,6}—remains to be elucidated.

While Sadek and Porrello focus on “cardiac rejuvenation,” the findings they describe also have direct relevance to the field of hPSC-based cardiac cell therapy. Indeed, preclinical studies in large animal models have shown that hPSC-derived cardiomyocytes can stably engraft and electromechanically integrate with host myocardium. However, these grafts consistently induce ventricular tachyarrhythmias.⁷ It is believed that these ventricular tachyarrhythmias are driven, at least in part, by the immature nature of the transplanted cardiomyocytes, which correspond to the early fetal stage.⁸ As a result, considerable effort is being deployed to develop protocols that promote the maturation of hPSC-derived cardiomyocytes. Studies like the one by Hirose and colleagues offer valuable insight that can help guide the development of such protocols. In fact, multiple studies have already demonstrated that treatment with triiodothyronine can promote the ultrastructural,

FIGURE 1. Regeneration of the neonatal mouse myocardium following apical resection.¹

electrophysiological, and metabolic maturation of hPSC-derived cardiomyocytes.⁹⁻¹¹ Whether transplantation of more mature cardiomyocytes will result in decreased arrhythmia burden is the object of active investigation.

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