See Article page e389.

Commentary: Great ideas come from the heart

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Luc de Clapiers, Marquis de Vauvenargues (1715-1747), gave us the aphorism in the title of this article. I suspect that Vauvenargues would have been surprised to see his words used in the context of tissue engineering. However, the heart is the focus of this commentary and regeneration of cardiac tissue after grievous injury (eg, infarction or exposure to a toxin) is a great idea.

Wang and colleagues¹ examine cardiac regeneration following a large myocardial infarction (MI) in neonatal rabbits (ie, leporine model) ranging in age from 1 day to 7 days after birth. The authors present data supporting the notion that the ability of neonatal leporine hearts to regenerate new myocardium after an acute MI progressively decreases from postnatal day 1 to day 4 and day 7. Their references include a report of a human neonate who recovered from post-MI cardiogenic shock, an important albeit single observation.²

Surgeons are in a unique position to incorporate novel regenerative therapies as adjuncts to conventional cardiac operations. Results to date with injections of growth factors, stem cell injections,³ or topical application of stem cells (eg, in fibrin sheets)⁴ are encouraging, but not ready for broad application. The field is advancing rapidly, as summarized by Braunwald.⁵ A novel model to study the transition of regenerative-capable to regenerative-incapable neonatal myocardium is therefore important. Understanding pivotal mechanisms for myocardial regeneration and devising methods to recruit them is foundational to this research. For example, the authors mention the Hippo pathway.¹ A review of the Hippo pathway illustrates the difficulty of

Luc de Clapiers, Marquis de Vauvenargues (1715-1747)

CENTRAL MESSAGE

The authors propose a leporine model for cardiac regeneration after MI. The goal is to understand cellular mechanisms in neonates then apply them to regenerate myocardium in mature post-MI hearts.

completely understanding much less modifying the ways signaling cascades work.⁶

As noted by the authors, “Molecular and cellular therapies to stimulate post-MI cardiac repair in adults appear to act via paracrine mechanisms and immunomodulation, and it is possible that the mechanisms of natural heart regeneration in neonates may intersect with that for exogenous therapies in adults through a shared immunologic pathway.”¹ Knowledge derived from a neonatal leporine model is potentially important for identifying candidate pathways for study and achieving the aforementioned goal of healing mature humans by regeneration.

Many questions remain. Do cells for regeneration arise from myocardial tissue or from another source (eg, bone marrow stem cells)? How will the new cells integrate with the existing myocardial cells? Will the newly formed syncytium have normal mechanical function? Will the syncytium of regenerated myocytes have normal electrical properties or will they be a source of arrhythmias? Will the formation of a new blood supply keep pace with the demands of the myocardium? Will the newly created interstitial tissues have normal compliance and thus avoid systolic bulging or diastolic dysfunction?

There are numerous lines of research underway to develop clinically relevant regenerative therapies for patients with cardiac disease. The novel leporine model described in this article is a preliminary and important step forward in the effort.

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