Cardiomyocyte replacement has been the focus of intense research because of the significant burden of heart failure. Although the adult mammalian heart is nonregenerative, recent studies have demonstrated that it retains a modest degree of cardiomyocyte turnover throughout life, mediated primarily by the proliferation of preexisting cardiomyocytes. In contrast to the adult heart, the neonatal mammalian heart possesses a remarkable regenerative ability in the first few days of life mediated by the proliferation of preexisting cardiomyocytes, after which cardiomyocytes permanently exit the cell cycle, and the regenerative ability of the heart is lost. Importantly, the embryonic mammalian heart also possesses a remarkable regenerative ability. Embryonic cardiomyocyte replacement studies were previously reported by the Cox and Torres groups. The Cox group showed that compensatory growth of cardiomyocytes occurred following cardiomyocyte ablation with the use of a holocytochrome c synthase–deficient model, whereas the Torres group demonstrated that cell competition promotes the silent exchange of cardiomyocytes without heart failure. Although these studies demonstrated that the fetal and early postnatal myocardium is capable of significant cardiomyocyte turnover and renewal, it remained unclear whether there is a limit to the regenerative capacity of the mammalian myocardium.

In this issue of Circulation, Sturzu and colleagues rigorously addressed the extent of embryonic heart regeneration following acute cardiomyocyte loss. They generated a genetic ablation model of cardiomyocytes in mouse embryonic hearts using a diphtheria toxin–based ablation system. They successfully eliminated cardiac progenitor cells or immature cardiomyocytes at various levels in the mouse embryonic heart. Nkx2.5-Cre or αMHC-Cre lines were crossed with a ROSA26 eGFP-DTA line, thereby resulting in ablation of Cre-expressing cells. The embryonic stem cells established from these Nkx2.5-Cre and αMHC-Cre blastocysts were injected into wild-type blastocysts to generate cardiac progenitor cell– or cardiomyocyte–ablated chimeric embryonic hearts, respectively. Taking advantage of blastocyst chimerism, chimeric embryos demonstrated successful ablation of cardiomyocytes to various degrees, from 0% to 95%. Intriguingly, the embryonic hearts were able to recover from substantial cardiomyocyte loss of up to 60% by using either cardiac progenitor cell or cardiomyocyte ablation, and they showed no signs of cardiac atrophy, hypertrophy, or dysfunction. Of note, previous studies of the genetic ablation of zebrafish cardiomyocytes showed a similar limit of myocardial regeneration, where ablation of up to 60% of cardiomyocytes was compatible with regeneration.

Although no comparable detailed quantification studies have been performed to assess the precise extent of neonatal heart regeneration, a recent report by the Lee group demonstrated that a larger neonatal heart resection injury, far <60% of the myocardium, is not compatible with complete regeneration in comparison with smaller injuries. Moreover, similar to previous neonatal injury studies, embryonic heart injury induced a significant increase in reactive cardiomyocyte proliferation, which supports the role of preexisting cardiomyocytes in embryonic heart regeneration. However, the absence of genetic fate–mapping studies in the current report makes it difficult to evaluate the potential contribution of noncardiomyocyte populations to embryonic heart regeneration.

Therefore, the fetal heart seems to have a more robust regenerative ability than the early postnatal heart, perhaps owing to the hypoxic intrauterine environment, which is critical for the maintenance of proliferative competency of cardiomyocytes. Mechanisms such as cell competition, contact or lateral inhibition, microRNAs, cyclins, transcription factors, DNA damage response, among others, have all been implicated in mammalian cardiomyocyte cell cycle regulation. However, the differences in cardiomyocytes as a substrate for these signals from embryonic to neonatal and adult hearts complicates the interpretation and translation of these studies. For example, the regulators of reactive cardiomyocyte proliferation in the embryonic heart may have minimal effects on cell cycle–arrested adult cardiomyocytes. Similarly, regulators of postnatal cell cycle arrest of cardiomyocytes may not be expressed in proliferative embryonic cardiomyocytes. Therefore, it would be important for future studies to examine the molecular mechanisms of context-dependent regulation of cardiomyocyte renewal in the mammalian heart.

Importantly, the current report, and others studying myocyte replacement in the fetal and early postnatal heart, as well, have started a debate in the field as to what exactly constitutes heart regeneration. Some biologists argue that myocyte replacement with the restoration of cardiac function and architecture does not correspond to regeneration if it occurs during intrauterine or postnatal development. We disagree. The de novo generation of tissue during organogenesis or growth is distinct from the regeneration of tissue after their loss, irrespective of the developmental or postnatal timeframe, even if they share some common features. The ability of the immature...
mammalian heart to regenerate and the subsequent loss of this ability provide an important tool for studying the aspects of regeneration that are not a part of normal development. For example, induction of myocyte proliferation above background levels, myocyte migration, epicardial activation, and injury-associated inflammation are all manifestations of the regenerative response that are superimposed on the underlying developmental or growth substrate.

The current report by Sturzu and colleagues is an important addition to the growing body of literature outlining the regenerative properties of the immature mammalian heart. These studies provide an invaluable tool for studying the intrinsic regenerative capacity of the mammalian heart and have already started to provide new mechanistic insights into the regulation of adult cardiomyocyte renewal.

Disclosures
None.

References

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Yuji Nakada, Wataru Kimura and Hesham A. Sadek

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