Editorial

Successful rebuilding after disaster, even in the heart, starts with infrastructure

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Mammalian heart regeneration has been the subject of intense debate and investigation among cardiovascular scientists for more than a century (1). While it is now widely accepted that the mammalian heart does have the capacity for self-renewal, replacement of injured tissue with new cardiomyocytes happens at a very low rate in the adult heart, and is not sufficient for the recovery of cardiac function after massive loss of cells (2).

Encouraged by work in non-mammalian vertebrates where organ regeneration occurs more predictably, scientists have taken a deeper look at the origin of cardiac muscle cells and identification of a cardiogenic differentiation program. Demonstration of cardiomyogenesis and the contribution of non-myocyte cells to heart regeneration stimulated investigation of the role of both exogenous and endogenous cells in heart repair (3). Several populations of circulating, cardiac tissue-resident progenitors, as well as non-cardiac progenitors have been identified by their ability to undergo cardiogenic differentiation and have been tested in animal models of heart disease as well as clinical trials (4). While these studies contributed significantly to our understanding of heart regeneration, they also identified limitations of the approach focused solely on cardiac muscle cells. Both endogenous and exogenous cardiac progenitors demonstrate low capability for cardiogenic differentiation and survival *in vivo*, thus highlighting the importance of local microenvironment-specific signaling and cell-cell interaction in heart regeneration (5-7).

Further progress in the field of heart regeneration is dependent on identification of the components of the cardiac regenerative niche—the microenvironmental milieu-associated with successful regeneration *in vivo*. A neonatal mouse heart regeneration model has been developed, offering the opportunity to understand and elucidate mechanisms for the mammalian heart regeneration *in vivo* (8). Because of its complexity—which includes technical difficulties of surgery in neonatal mice, partial resection of myocardium and transient regenerative potential of neonatal hearts—the degree of heart regeneration is debated (9). In this issue of *The Journal of Thoracic and Cardiovascular Surgery*, Ingason *et al.* (10) present data examining a timeline for regeneration of myocardium in this neonatal mouse model. The authors not only confirmed previous work demonstrated the high regenerative capacity of neonatal mouse heart (8), but also have made several important observations on the timeline of proliferation and migration of cardiac muscle cells and endothelial cells during heart regeneration. One day old CD-1 mice underwent apical resection of the heart via a left anterolateral thoracotomy under hypothermic circulatory arrest. The authors showed that neonatal cardiac apex resection did not increase the amplitude of proliferative response, but prolonged the period of high proliferative activity of cardiomyocytes and endothelial cells over one week—in contrast to the first few days found in sham—indicating that mechanisms of postnatal cardiomyocyte cell cycle withdrawal appear to be delayed by apical resection in neonatal mouse heart. Since myocardial infarction induces dedifferentiation and proliferation of cardiomyocytes (11), identification of strategies to prevent cell cycle withdrawal

in general may help to promote regeneration after ischemic heart injury.

This study (10) has also demonstrates that an early event after injury is migration of endothelial cells into the apical thrombus, leading to formation of functional arteries. Arteries form within one to five days after apical resection. Another interesting observation from this study is that cardiomyocyte ingrowth followed on the footsteps of the advancing blood vessels. In a supporting *in vitro* study, co-culture of cardiomyocytes and human umbilical vein endothelial cells also demonstrated that the heart muscle cells aligned themselves with the organizing endothelial cells. This finding adds to growing evidence to suggest that the perivascular space represents a "regenerative niche" which provides supply of both endothelial cells and cardiac muscle cells for heart regeneration (12).

Understanding the mechanisms involved in blood vessels ingrowth during mouse heart regeneration is an important step in developing new approaches to treat multiple cardiovascular diseases associated with insufficient angiogenesis. Attempts at growing new blood vessels using genes, miRNA, proteins, and cells have had modest success in patients. A number of clinical trials including VIVA (recombinant human VEGF) (13), BOOST (autologous bone-marrow cells) (14), POSEIDON (human bone marrow-derived mesenchymal stem cells) (15), IMPACT-CABG (autologous CD133+ stem cells) (16), and CADUCEUS (cardiosphere-derived cells) (17) have shown some incremental improvement in symptoms and/or selected measurements of cardiac function. However, no studies have demonstrated the robust repair and regeneration sought by patients with severe heart disease and their clinicians. Interestingly, many pre-clinical studies performed in young healthy animals have shown greater promise (18). One explanation for this discrepancy is that comorbid disease seen in our patients including diabetes, hypertension, and dyslipidemia lead to elaboration of anti-angiogenic factors that are not seen in most animal models (19,20). Newer models of ischemic heart disease in the setting of comorbid diseases have helped elucidate these processes (21-23).

This is a well performed study with superb technical work in a challenging animal model and sound supporting science. It provides an incremental mechanistic understanding of the process of myocardial regeneration in the post-natal mammalian heart. The authors put forth a hypothesis that a single chemokine may be governing the coordinated angiogenesis and cardiomyocyte migration observed during regeneration. Further work identifying the signaling pathways responsible will be important if we are to guide/manipulate the progression. There are of course limitations to the work, and the poor correlation to the ischemic and injured adult human heart. The thrombus observed after apical resection in a neonatal mouse is not completely analogous to the injury pattern observed in acute or chronic myocardial ischemia. Similar experiments in an adult myocardial infarction model would be interesting. As discussed above, the effect of common comorbid diseases will likely also impact how the heart responds to injury.

There are other things to ponder in looking at these results, like the clot that forms upon apical resection. In the mouse, Ingason and colleagues observe the sequence of events as injury → thrombosis → fibrosis → angiogenesis → cardiomyogenesis. What is the role of thrombosis in this process? While one can argue this is simply to allow hemostasis in the injured heart, it is possible that thrombosis is a critical step in regeneration. The idea that clot-derived factors may promote tissue recovery, including the heart, has been under investigation for some time (24). The cardiovascular community has been committed to suppressing intravascular thrombosis for obvious reasons. Perhaps we should also be turning our attention to the concept that extravascular thrombosis is of potential value, and considering ways of promoting this to modify the interstitial microenvironment in a way that promotes myocardial regeneration.

A key takeaway from Ingason and colleagues is the development of a better understanding of the timing and order of the heart's successful repair after injury. Development of successful clinically useful cardiac repair strategies may similarly require stimulating new vessel formation prior to attempting delivery of cardiomyocytes or progenitor cells. Correcting the angiogenesis deficit associated with diseased conditioned, and making the microenvironment conducive to angiogenesis needs more attention. When a community is recovering from a natural or manmade disaster, the roads and infrastructure are critical steps in successful restoration—it appears that the heart is the same.

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Footnote

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to declare.

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