Editorial

See related article, pages 1226–1237

Curiosity Killed the Cat and Found New Myocytes

Mark A. Sussman

Not very long ago when I set up my first research laboratory in the early 1990s, the prevailing wisdom was that new myocyte formation in the mature myocardium was nonexistent or occurred with about the same frequency as an appearance of Halley’s comet.1–3 Occasional sightings of myocytes undergoing what appeared to be mitotic division1,5 in adult tissue sections were compared to the proverbial “needle in a haystack” and often dismissed as biologically irrelevant in terms of cardiomyocyte replacement or myocardial repair.4 In short, the heart was a postmitotic organ with essentially no capacity for new myocyte formation. If only there were cells that possessed the capability for de novo formation of cardiomyocytes and vasculature, then perhaps we could repair pathological injury in the heart. Researchers tried to force myocytes to divide using molecular maneuvers,7,8 force neonatal myocytes to engraft into mature hearts,9 and even force chimeric marriage between skeletal muscle and the heart in attempts to restore contractile function.10–11 A lot of hearts were broken, but we were not doing a very good job of fixing them.

Amazing what a difference a decade can make. After years of searching for the source of new myocyte formation, it turns out that while isolating adult and neonatal myocytes, we had been “throwing the baby out with the bathwater.” In retrospect, it seems so obvious. Precursors for new myocyte formation did not look much like muscle cells, were relatively rare and small, and needed to be coaxed into revealing themselves by examining myocardial biology with a different and novel perspective. In the end, the elusive basis for regeneration and repair in the heart was reminiscent of other tissues: stem cells. And since then, all manners of hell have broken loose with debates on (but not restricted to) the biological relevance, cell type, and origin of stem cells found in the myocardium. Whether you are a zealous advocate or confirmed skeptic, the field of myocardial regeneration is an easy place to find lack of consensus, strong opinions, and a multitude of experimental interpretations.12–17 Now in this issue of Circulation Research, Angert et al18 strike a blow in support of the c-kit+ stem cell camp with their observations of myocyte formation following pathological injury in the feline heart.

In a study that relies essentially on histological evidence obtained in the wake of isoproterenol-induced diffuse myocardial injury, Angert et al used a simple but elegant approach to tag proliferating cells and track their fate: controlled pulsing of the DNA analog bromodeoxyuridine (BrdU) at various phases of the injury and recovery process. They arbitrarily divided the timeline into the injury, early recovery, and late recovery phases at 10, 17, and 38 days, respectively. The injury phase consisted of bombarding the heart with a chronic minipump infusion of isoproterenol for 10 days, which makes for a very unhappy heart characterized by depressed contractile function, chamber dilation, myocyte hypertrophy, and fibrosis. After 10 days the isoproterenol pump was removed and the heart was watched for signs of cellular replacement. The proliferation of cells was tracked during the 3 time points by a week of BrdU incorporation before sacrifice coupled with immunocolocalization of typical markers such as c-kit for stem cells and sarcomeric markers for myocytes. Results show that in the injury phase the BrdU label appeared in the c-kit+ stem cells, but not myocytes. Then as proliferation slowed during the recovery phase, BrdU label incorporated early on into nonmyocytes appeared in the myocyte population. The authors conclude on the basis of their collective findings that a c-kit+ cardiac myocyte precursor pool stimulated in response to injury gives rise to new myocytes in the recovery phase weeks later.

Before the corks get popped on the champagne bottles and the c-kit+ cell camp celebrates, some sobering unanswered questions will need to be resolved. Two words come to mind: “smoking gun.” Although the simplest explanation of the Angert et al19 report is consistent with cardiomyogenesis from c-kit+ stem cells, the evidence is purely circumstantial. Using BrdU as a label, it is not possible to unequivocally trace the stem cells from injury to recovery; rather, BrdU provides only snapshots in time. Fans of lineage tracing studies would argue that the c-kit+ population would need to be specifically tagged during injury and then followed into myocytes rather than using a marker for cell proliferation that does not discriminate between cell types. Of course, such studies are not readily accomplished in a large animal model such as the cat for which genetic engineering is a major stumbling block. However, the Angert et al findings are consistent with those previously reported for myocyte replacement in the mouse following pathological injury.19 Labeling of proliferating cells in the adult heart has consistently shown that myocytes possess severely limited replicative capacity, so it makes intuitive sense that if myocyte formation occurs, the source has to be from some other cell type, and the implication here is that c-kit+ cells are contributing to de novo myogenesis. One additional facet that

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From the San Diego State University Heart Institute and Department of Biology, San Diego, California.

Correspondence to Mark A. Sussman, PhD, Heart Institute, Department of Biology, San Diego State University, NLS 426, 5500 Campanile Drive, San Diego, CA 92182. E-mail sussman@heart.sdsu.edu

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would have been nice to see in this study is a correlation between BrdU labeling and myocyte size, with the assumption that smaller myocytes are “younger,” as previously published by this and other groups.20,21

Lest we not forget, the experimental model is also open to attack from the critics. Isoproterenol-induced cardiomyopathy was rationally justified as a model of reliable, reproducible, diffuse injury that can be rapidly terminated. Those same characteristics are also what distinguish this cardiomyopathy from the acute damage induced by infarction or chronic progressive stress occurring from coronary artery disease or hypertension. One intriguing possibility not considered by the authors is that isoproterenol exposure may exert mitogenic effects on the c-kit+ cells and drive their expansion in the wake of the injury. It is certainly true that c-kit+ cells expand in cardiomyopathic injury and aging. Adrenergic drive has also been associated with proliferation of certain cell types, including stem cells. Until we have a better handle on what signals promote stem cell expansion, commitment, engraftment, and persistence, we cannot assume that signals that are bad for cardiomyocytes also impaire the stem cell pool. The effect of the isoproterenol may be either direct or indirect drive, but it may prime the c-kit+ cell population in an unnatural way that boosts the precursor cell population for the proliferative labeling by BrdU.

The cat is unusual in that myocardial infarction produces relatively little damage because of robust collateral circulation. Felines have evolved a mechanism to give their hearts superior resistance to the sort of pathological challenge that would typically kill a man. Maybe such supernormal coping strategies helped promulgate the legend of a cat having 9 lives. But to paraphrase the old saying, scientific curiosity and persistence, we cannot assume that signals that are bad for cardiomyocytes also impair the stem cell pool. The effect of the isoproterenol may be either direct or indirect drive, but it may prime the c-kit+ cell population in an unnatural way that boosts the precursor cell population for the proliferative labeling by BrdU.

Disclosures
None.

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