Big Cells, Little Cells, Stem Cells
Agents of Cardiac Plasticity

Eduardo Marbán

As of August 2003, the prevailing dogma posited that the heart is a terminally-differentiated organ, that the myocytes we have now are those we were born with (only bigger), and that the best hope for treating cardiac injury is to limit the insult (eg, by prompt reperfusion) or to block secondary maladaptive pathways. Because of pioneering work from various laboratories,1-3 the concept of cardiac plasticity has come to replace the old static-organ dogma. We now believe that the normal adult heart is the net result of a slow rate of cell loss balanced by ongoing cell replacement. The predominant mode of cell loss is via apoptosis, reflecting the normal processes of wear and tear. Cell replacement, on the other hand, taps into a reservoir of resident cardiac stem cells (CSCs). Such CSCs lurk in niches distributed inhomogeneously throughout the heart,4 and, when activated, enter the mitotic cycle to eventually become cardiomyocytes and vascular cells. Back-of-the-envelope calculations, based on the observed frequencies of apoptotic events and mitotic figure in heart tissue, lead us to estimate that cardiac myocytes turn over several times in a typical mammalian lifespan. While lamenting our complacency (how could we have missed [or dismissed] the evidence supporting turnover for so long?), it is important to recognize that the processes are slow and, statistically speaking, rare: CSCs comprise only 1 of 30,000 cells in the heart.5 On a more positive note, it is wondrous to observe how thoroughly the landscape has been transformed in less than four years.

Compelling though the evidence is for cardiac plasticity, some key parts of the puzzle have been conspicuously missing. If the heart is constantly self-renewing, where are the “new” cardiac myocytes and vascular cells that arise as CSCs differentiate? What are the physiological properties of the new myocytes? How many are there? Does the CSC regenerative pathway figure in normal cardiac growth? In a landmark article in this issue of Circulation Research6, House, Anversa and their collaborators go a long way toward filling in the missing pieces. Within the postnatal feline heart, they identify 2 subpopulations of cardiac myocytes: fully-developed “big cells” with 2 nuclei, and mononuclear “little cells”. The little cells are electrically excitable, cycle calcium and beat, but they are distinctive in that, unlike the big cells, they express T-type calcium channels. The little cells also have slower calcium transients and a lower density of transient outward current than the big cells, reminiscent of the cardinal pathophysiological changes associated with myocytes isolated from patients or animals with heart failure.6-11 In vitro evidence is discussed, but not presented in full, to the effect that c-kit+ CSCs isolated from the cat heart can become little myocytes when cocultured with neonatal rat heart cells (Tom and Jerry take note). Little cells are more often Brdu+ and have a somewhat higher telomerase activity than big cells, suggesting that they are more proliferative. Thus, the little cells presumably are newly-hatched myocytes, the missing links between CSCs and mature heart cells. Read the article. There is more, including a critical calculation arguing that postnatal growth of the heart is due largely to myocyte proliferation, not just myocyte hypertrophy.

As with all groundbreaking articles, more questions arise than are answered. Missing here is evidence of new vascular cells arising endogenously within the heart, or from c-kit+ cells in culture; also lacking is any evidence that little cells actually go on to become big cells. Might they be in a state of arrested development? It is curious and counterintuitive that the percentage of little cells is identical and fairly high (11.5%) at 11 weeks and 22 weeks, despite the fact that the heart doubles in size over that interval. If CSCs produce little cells which go on to become big cells, one might conjecture that the proportion of little cells would fall over time to some asymptotic frequency at which the creation of new cells just offsets the very low rate of apoptosis (quantified at only 0.08% in the present work). Perhaps the 22 week time point studied here is still far from the steady state that would be reached in mid-adulthood.

The recognition that the heart is not static but rather sustains turnover and self-repair has opened up dramatic new possibilities for therapeutics. If the heart has the capacity to renew itself, perhaps that capacity can be tapped to achieve iatrogenic regeneration, in those cases where catastrophic events such as myocardial infarction have outstripped the heart’s endogenous repair capacity. Methods have already been developed to harvest stem cells from a patient’s own heart using minimally-invasive methods; millions of transplantable cells can be grown in vitro, creating a very specific paradigm for autologous therapeutics.12 Soon we may be able to grow “little cells” from transplanted CSCs within the diseased human heart, with a view to restoring functional capacity.

Take a minute to catch your breath. Never has cardiobiology been more exciting than it is now.

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References

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