Cell Stem Cell
Previews

Rewind to Recover: Dedifferentiation after Cardiac Injury

Edward E. Morrisey[1,*]
[1]Department of Medicine and Department of Cell and Developmental Biology, Institute for Regenerative Medicine, Cardiovascular Institute, Translational Research Center, Room 11-124, 3400 Civic Center Boulevard, Building 421, University of Pennsylvania, Philadelphia, PA 19104-5129, USA
*Correspondence: emorrise@mail.med.upenn.edu
DOI 10.1016/j.stem.2011.10.011

In adult mammals, cardiomyocytes are known to reactivate an embryonic gene-expression program after injury. In this issue of *Cell Stem Cell*, Kubin et al. (2011) show that oncostatin M regulates this dedifferentiation which, while beneficial for recovery from acute injury, if persistent results in heart failure in both rodents and humans.

Heart disease is the leading cause of death in the Western world; therefore, understanding how the adult heart responds to common injuries, such as myocardial infarction (MI) or dilated cardiomyopathy (DCM), is a crucially important research question. The mammalian heart has a very limited range of responses to injury and stress, but most insults ultimately lead to cardiomyocyte hypertrophy (an increase in cell size but not cell division) or cardiomyocyte dropout induced by apoptosis. Although the mammalian heart cannot robustly regenerate after cardiomyocyte proliferation ceases, postnatal cardiomyocytes do dedifferentiate after injury and re-express markers of embryonic cardiomyocytes similar to what occurs in zebrafish hearts, which regenerate efficiently after injury. The underlying mechanism regulating this dedifferentiation, and its role in the response to cardiac injury, is largely unknown. In the current issue of *Cell Stem Cell*, Kubin et al. (2011) characterize the signaling pathways leading to mammalian cardiomyocyte dedifferentiation after injury. They show that the inflammatory cytokine oncostatin M (OSM) is induced at high levels in human patients with DCM and that exposure of rodent cardiomyocytes to OSM increases Erk1/2 signaling, which leads to a variety of responses including re-expression of embryonic heart markers such as smooth muscle α-actin. Interestingly, Kubin et al. (2011) also observed increased or ectopic expression in OSM-treated adult cardiomyocytes of several stem cell genes including *Runx1*, *c-kit*, and *Dab2*. Using a chronic mouse model of increased cardiac macrophage infiltration, which recapitulates major features of human DCM, the authors also show improved cardiac function after genetic loss of OCM signaling. When using a model of acute ischemic injury, however, the authors found that genetic loss of OCM signaling resulted in a worsening of cardiac function leading to increased lethality. Together, these data suggest that OCM confers a protective signal during the early stages of cardiac injury and repair by promoting cardiomyocyte dedifferentiation, potentially by activating a stem cell gene-expression signature. However, persistent OCM signaling, such as might occur in chronic heart conditions, prevents cardiomyocytes from redifferentiating, which is important to maintain contractile force and function.

One of the more interesting findings from Kubin et al. (2011) is the increased expression of stem cell markers Runx1, c-kit, and Dab2 in OCM-treated cardiomyocytes. A previous report showed that Runx1 was upregulated in human and rat myocardium after ischemic injury, which may account for the increase observed after OCM treatment (Gattenlöhner et al., 2003). Dab2 is a target of GATA transcription factors and its OCM-induced increase may reflect increased expression or activity of GATA4/6, which has been reported during cardiac hypertrophy (Molkentin et al., 1998; Morrisey et al., 2000; van Berlo et al., 2010). c-kit has been used as a surrogate cardiac stem/progenitor marker, and there is much interest in identifying cardiac stem cells in the postnatal heart in the hopes of improving cardiac repair after injury (Beltrami et al., 2003). However, whether a postnatal cardiac progenitor exists that is capable of generating new myocardium after injury remains unclear. Kubin et al. (2011) show that c-kit is upregulated in response to OCM treatment, which could be interpreted as increased activation of a postnatal cardiac stem cell population. The implication from some previous studies on c-kit-positive cells in the adult myocardium is that they act as resident cardiac stem cells that robustly respond to injury and generate new tissue. However, if this is true, it is hard to reconcile these findings with the almost complete inability of the adult mammalian heart to regenerate after injury. With the current paper in mind, previous findings of a c-kit-positive population of cardiomyocytes acting as a stem cell population could be reinterpreted. c-kit-positive cells may normally exist at low levels in the postnatal heart, but, rather than defining a stem cell population, they may represent dedifferentiated cardiomyocytes. What these dedifferentiated cardiomyocytes are doing in the postnatal heart is unclear, but they may be present at a stochastic level and increase in response to injury or stress, which could make them appear to act as cardiac stem cells in the adult heart.

Because the mammalian heart has such a limited ability to respond to injury and lacks overt regenerative capacity, one of the "holy grails" of current cardiac stem cell research is a method to promote cardiomyocyte proliferation in the setting of acute or chronic injury. The current report by Kubin et al. shows that OCM signaling does promote a pro-proliferative

response due, at least in part, to increased Erk1/2 signaling. Previous reports have shown that Fgf signaling promotes proliferation of embryonic cardiomyocytes and Erk1/2 acts downstream of Fgf signaling in this process (Engel et al., 2006). Kubin et al. (2011) show that combined treatment of cardiomyocytes with Fgf2 and OCM increased entry into S-phase more efficiently than treatment with individual factors. Thus, in response to OCM treatment, cardiomyocytes do dedifferentiate and try to proliferate. As yet unknown blocks to cell cycle re-entry are still present, however, preventing a robust proliferative response to OCM.

Pathways that regulate the dedifferentiated state of cardiomyocytes are clearly important and may eventually lead to methods to promote cardiomyocyte replacement after injury in the human heart. The major roadblock to such an approach still appears to be the inability of cardiomyocytes to fully re-enter the cell cycle. Although increased cardiomyocyte cell division after treatment with neuregulin or ErbB4 has been reported, the overall effect is still rather low (i.e., approximately 0.6% of cardiomyocytes in vivo responded to these treatments) (Bersell et al., 2009). Cardiomyocytes need to maintain proper contractile function or the biomechanics of the heart will fail. Although lower vertebrate cardiomyocytes do go through a process of dedifferentiation, proliferation, and redifferentiation to repair injury, the high cardiac output in mammalian hearts may preclude such a mechanism as it could lead to a lethal drop in cardiac output because of decreased contractility. The finding that OCM promotes dedifferentiation, however, may help lead to approaches that could promote dedifferentiation and ultimately increase cardiomyocyte replacement after injury-induced loss in humans.

ACKNOWLEDGMENTS

Studies in the Morrisey Lab are supported by funding from the National Institutes of Health (HL100405) and the American Heart Association Jon Holden DeHaan Myogenesis Center grant.

REFERENCES

Beltrami, A.P., Barlucchi, L., Torella, D., Baker, M., Limana, F., Chimenti, S., Kasahara, H., Rota, M., Musso, E., Urbanek, K., et al. (2003). Cell *114*, 763–776.

Bersell, K., Arab, S., Haring, B., and Kühn, B. (2009). Cell *138*, 257–270.

Engel, F.B., Hsieh, P.C., Lee, R.T., and Keating, M.T. (2006). Proc. Natl. Acad. Sci. USA *103*, 15546–15551.

Gattenlöhner, S., Waller, C., Ertl, G., Bültmann, B.D., Müller-Hermelink, H.K., and Marx, A. (2003). Am. J. Pathol. *163*, 1081–1090.

Kubin, T., Pöling, J., Kostin, S., Gajawada, P., Hein, S., Rees, W., Wietelmann, A., Tanaka, M., Lörchner, H., Schimanski, S., et al. (2011). Cell Stem Cell *9*, this issue, 420–432.

Molkentin, J.D., Lu, J.R., Antos, C.L., Markham, B., Richardson, J., Robbins, J., Grant, S.R., and Olson, E.N. (1998). Cell *93*, 215–228.

Morrisey, E.E., Musco, S., Chen, M.Y., Lu, M.M., Leiden, J.M., and Parmacek, M.S. (2000). J. Biol. Chem. *275*, 19949–19954.

van Berlo, J.H., Elrod, J.W., van den Hoogenhof, M.M., York, A.J., Aronow, B.J., Duncan, S.A., and Molkentin, J.D. (2010). Circ. Res. *107*, 1032–1040.

Guiding DNA Methylation

Alexander Meissner[1,2,3,*]
[1]Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA 02138, USA
[2]Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA
[3]Harvard Stem Cell Institute, Cambridge, MA 02138, USA
*Correspondence: alexander_meissner@harvard.edu
DOI 10.1016/j.stem.2011.10.014

How DNA methyltransferases, with their limited target specificity, establish cell-type-specific epigenetic patterns is poorly understood. Schübeler and colleagues (Lienert et al., 2011) now show that methylation-determining regions (MDRs) within promoter regions are sufficient to recapitulate endogenous patterns and dynamics of DNA methylation.

DNA methylation of CpG dinucleotides is required for normal mammalian development. Most of the genome contains few CpGs and they tend to be methylated across all cell types. Unmethylated CpGs are typically found in clusters called CpG islands (CGIs), which comprise about 1%–2% of the genome. About half of CGIs in mouse and human are associated with transcription start sites (Deaton and Bird, 2011), and many are linked to housekeeping genes and developmental regulators. While the enzymes responsible for establishing and maintaining DNA methylation have been well-studied and genome-scale data sets continue to shed light on its genomic distribution (Meissner, 2010), it remains less clear how particular sites in the genome are protected and others are targeted for maintenance or de novo methylation. None of the three catalytically active DNA methyltransferases (Dnmt1, 3a, and 3b) shows a particular target preference that could explain cell-type-specific methylation patterns, suggesting that alternative mechanisms must be in place to either direct or inhibit their recruitment.

In a recent issue of *Nature Genetics,* Schübeler and colleagues set out to further