Daniela Cesselli and Antonio Paolo Beltrami

Stem Cell Senescence in Diabetes: Forgetting the Sweet Old Memories

Diabetes 2014;63:1841–1843 | DOI: 10.2337/db14-0275

Diabetic cardiomyopathy is identified by a left ventricular dysfunction due to metabolic and cellular abnormalities in the absence of atherosclerosis or hypertension and is one of the leading causes of morbidity and mortality in the diabetic population (1). It is characterized by myocardial necrosis and fibrosis, endothelial dysfunction, and stem cell senescence (2). This latter phenomenon is now considered to be a central mechanism of aging and age-related pathologies as it has been associated with the reduced ability of tissues to replace lost cells and to repair damage (3,4). In this issue, Vecellio et al. (5) analyzed the intriguing issue of whether stem cells isolated from diabetic hearts have a metabolic memory reminiscent of their original milieu. The term metabolic memory was first used to describe the persistent development of diabetes complications that intervenes even after glycemic control has been achieved (6). Recent studies have suggested that the epigenetic changes that occur in cells exposed to hyperglycemia may be responsible for this phenomenon (6).

Epigenetics may be defined as a heritable phenotype that does not depend on the primary sequence of DNA. This trait may involve its heritability through mitosis or meiosis (7). Chromatin is an orderly nucleoprotein assembly that results from the packaging of DNA with histone and nonhistone proteins (8). Eukaryotic chromatin may be viewed as a series of superimposed organizational layers. The first organizational layer consists of the chemical modifications of nucleotides (e.g., methylation and methyl oxidation of cytosine) (8). Histone variants and their posttranslational modifications (PTMs) compose the second organizational layer (8). Finally, the third layer of organization consists in the nuclear compartmentalization of chromatin (9,10). A large number of histone PTMs have been described (including acetylation, methylation, ubiquitylation, sumoylation, and phosphorylation). Accordingly, several scientists have postulated that a histone code exists, where different histone modifications act sequentially or in combination and are read by other proteins ("readers") to bring about downstream effects (11). These PTMs of histones are carried out by different classes of enzymes that act either as chromatin "writers" (e.g., histone acetyltransferases, histone methyltransferases, histone ADP ribosyltransferases) or "erasers" (e.g., histone deacetylases, histone demethylases) (11).

Vecellio et al. (5) isolated and expanded in vitro cardiac mesenchymal stem cells (CMSC) obtained from the atrial appendages of 22 patients undergoing coronary artery bypass grafting (CABG) or angioplasty. The biologic characteristics, DNA methylation, and histone PTM of CMSC obtained from 11 type 2 diabetic patients (D-CMSC) were then compared with those of CMSC derived from 11 normoglycemic patients (ND-CMSC). The authors observed that diabetes impairs CMSC proliferation and differentiation, increasing their rate of cellular senescence. These biologic alterations were associated with a modification of D-CMSC chromatin landscape. Specifically, D-CMSC are characterized by increased trimethylation of histone H3 lysine 9 and lysine 27 and histone H4 lysine 20, decreased monomethylation of histone H3 lysine 9, and reduced acetylation of histone H3 lysine 9 and lysine 14 and histone H4 lysine 16. Functionally, these PTMs are associated with a closed chromatin structure, which is less accessible to transcription factors leading to gene repression. Intriguingly, repressive chromatin and CpG island DNA hypermethylation were detected at promoters of genes involved in cell growth and genomic stability, paralleling the reduced expression of these genes in D-CMSC. In this line, several epigenetic enzymes (including histone demethylase JMJD3, histone methylases Suv420H1, SETD-7, methyl CpG binding protein-2, and 5 general control of amino acid synthesis [GCN5]–related N-acetyltransferases [GNAT] acetylases GCN5 and p300/CBP–associated factor [PCAF]) were differentially expressed

Department of Medical and Biological Sciences, University of Udine, Udine, Italy
Corresponding author: Antonio Paolo Beltrami, antonio.beltrami@uniud.it.

See accompanying article, p. 2132.

in D- and ND-CMSC. The authors experimented with the ability of the proacetylation compound histone acetylase activator pentadecylidenemalonate 1b (SPV106), an activator of the GCN5A/PCAF members of the GNAT family, to reverse the epigenetic landscape of D-CMSC. SPV106 partially rescued the histone acetyltransferase activity of D-CMSC, increased histone acetylation (H3K9Ac, H3K14Ac, and H4K16Ac), and decreased DNA methylation at promoter CpG islands, without affecting the global histone methylation level. Remarkably, these epigenetic changes were associated with a reduction in the rate of cell senescence, a recovery in the proliferation ability, and a partial rescue of the differentiation capacity of D-CMSC (Fig. 1).

Vecellio et al. newly describe a mechanism through which the epigenetic memory of hyperglycemia conveys to human stem cell senescence and dysfunction. Most important, the authors demonstrate that a short drug treatment with SPV106 is able to partially reverse the modified epigenetic landscape of D-CMSC, rescuing their proliferation and differentiation abilities. One potential

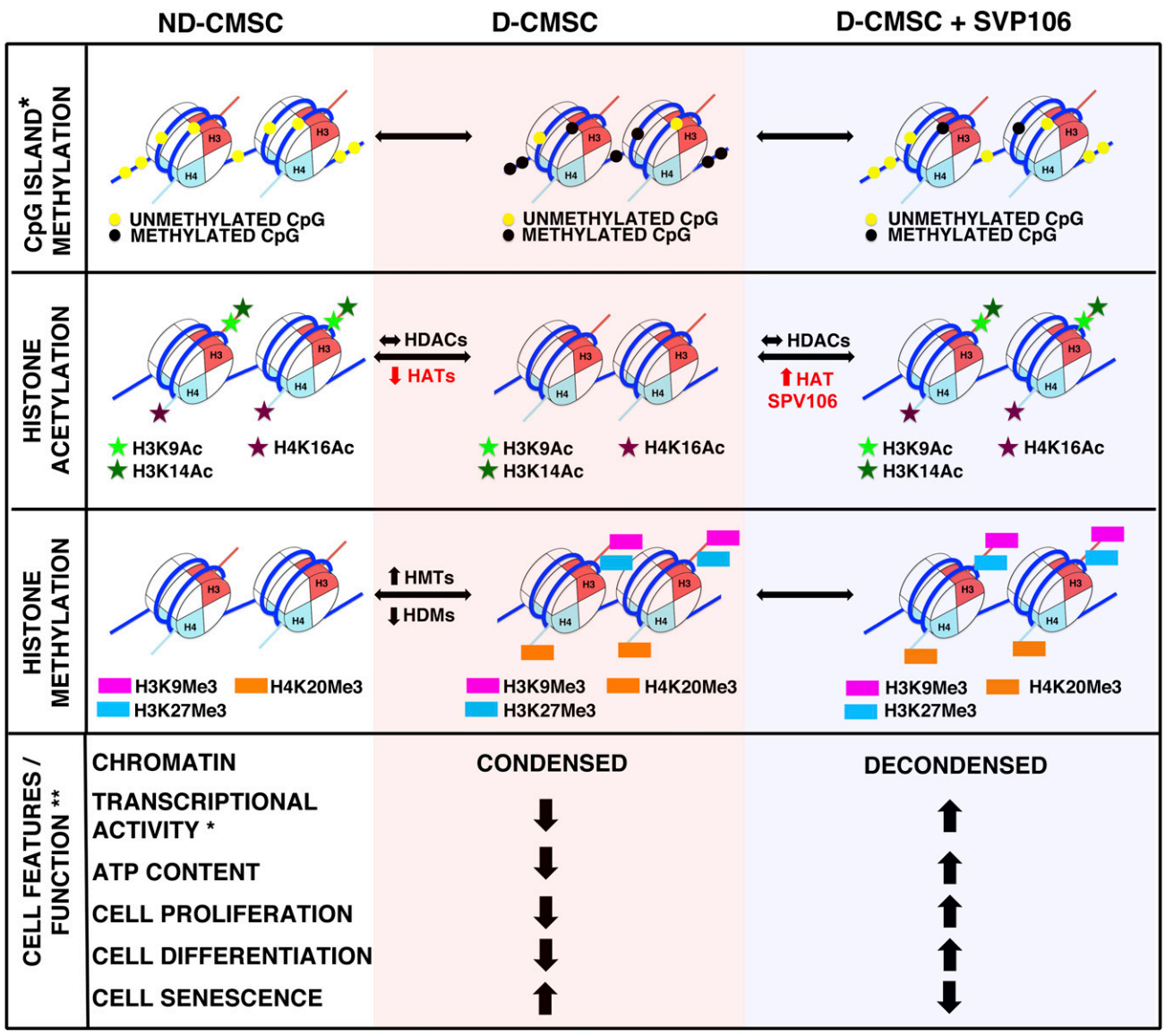

Figure 1—Schematic depiction of the differences in CpG island methylation, histone modifications, epigenetic enzymes activity, and cell features characterizing human CMSC obtained from normoglycemic and diabetic hearts. The treatment of D-CMSC with the proacetylation compound SPV106 partially reverts the epigenetic changes characterizing D-CMSC and restores some impaired cell functions. *Genes known to be associated to proliferation and genome stability. **Arrows refer to D-CMSC vs. ND-CMSC (second column) and to D-CMSC vs. SPV106-treated D-CMSC (third column). H3K9Ac, acetylation of histone H3 lysine 9; H3K14Ac, acetylation of histone H3 lysine 14; H4K16Ac, acetylation of histone H4 lysine 16; H3K9Me3, trimethylation of histone H3 lysine 9; H3K27Me3, trimethylation of histone H3 lysine 27; H4K20Me3, trimethylation of histone H4 lysine 20; HAT, histone acetyltransferases (GCN5A/PCAF members of the GNAT family); HDAC, histone deacetylases (class I, II, and III); HDM, histone demethylases (JMJD3); HMT, histone methylases (Suv420H1, SETD-7, and methyl CpG binding protein-2).

limitation of this work is, as stated by the authors, the limited number of samples analyzed that may have precluded a more in-depth insight into the metabolic impact of lysine acetylation in the onset of insulin resistance and diabetes. Furthermore, the control subjects that were used (ND-CMSC) were collected from pathologic hearts. In the future, a comparison of D- and ND-CMSC with similar cells obtained from normal hearts could help in distinguishing epigenetic changes that are typical of diabetic cardiomyopathy from those shared with cardiac ischemia, possibly opening the way to more targeted epigenetic interventions. Moreover, the evaluation of the potential ability of SPV106 to antagonize stem cell senescence and dysfunction in vivo is the next required step toward the clinical application of this work.

Early phase clinical trials that experimented with the use of cardiac-derived stem cells have shown exciting but preliminary results (12,13). However, aging, pathology (14), and, as elegantly shown in Vecellio et al. (5), diabetes may alter the biologic characteristics of human cardiac primitive cells, thus potentially reducing their in vivo reparative ability. The identification of drug treatments able to erase the memory of a pathologic state may increase the efficacy of stem cell–based therapy.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Falcão-Pires I, Leite-Moreira AF. Diabetic cardiomyopathy: understanding the molecular and cellular basis to progress in diagnosis and treatment. Heart Fail Rev 2012;17:325–344

2. Delucchi F, Berni R, Frati C, et al. Resveratrol treatment reduces cardiac progenitor cell dysfunction and prevents morpho-functional ventricular remodeling in type-1 diabetic rats. PLoS One 2012;7:e39836

3. Beltrami AP, Cesselli D, Beltrami CA. Stem cell senescence and regenerative paradigms. Clin Pharmacol Ther 2012;91:21–29.

4. Baker DJ, Wijshake T, Tchkonia T, et al. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature 2011;479:232–236

5. Vecellio M, Spallotta F, Nanni S, et al. The histone acetylase activator pentadecylidenemalonate 1b rescues proliferation and differentiation in the human cardiac mesenchymal cells of type 2 diabetic patients. Diabetes 2014;63:2132–2147

6. Jayaraman S. Epigenetic mechanisms of metabolic memory in diabetes. Circ Res 2012;110:1039–1041

7. Berger SL, Kouzarides T, Shiekhattar R, Shilatifard A. An operational definition of epigenetics. Genes Dev 2009;23:781–783.

8. Zhou VW, Goren A, Bernstein BE. Charting histone modifications and the functional organization of mammalian genomes. Nat Rev Genet 2011;12:7–18

9. Lieberman-Aiden E, van Berkum NL, Williams L, et al. Comprehensive mapping of long-range interactions reveals folding principles of the human genome. Science 2009;326:289–293

10. Goetze S, Mateos-Langerak J, Gierman HJ, et al. The three-dimensional structure of human interphase chromosomes is related to the transcriptome map. Mol Cell Biol 2007;27:4475–4487

11. Gardner KE, Allis CD, Strahl BD. Operating on chromatin, a colorful language where context matters. J Mol Biol 2011;409:36–46

12. Chugh AR, Beache GM, Loughran JH, et al. Administration of cardiac stem cells in patients with ischemic cardiomyopathy: the SCIPIO trial: surgical aspects and interim analysis of myocardial function and viability by magnetic resonance. Circulation 2012;126(Suppl. 1):S54–S64

13. Malliaras K, Makkar RR, Smith RR, et al. Intracoronary cardiosphere-derived cells after myocardial infarction: evidence of therapeutic regeneration in the final 1-year results of the CADUCEUS Trial (CArdiosphere-Derived aUtologous stem CElls to reverse ventricULar dySfunction). J Am Coll Cardiol 2014;63:110–122

14. Cesselli D, Beltrami AP, D'Aurizio F, et al. Effects of age and heart failure on human cardiac stem cell function. Am J Pathol 2011;179:349–366