Cardiomyocyte Renewal in Humans

To the Editor:

In a recent review article by Leri, Kajstura, and Anversa\(^1\) in Circulation Research, there are several misrepresentations and factual errors in the description of our study on birth dating of heart cells.\(^2,3\) These errors affect their conclusions, and it is thus important to make some clarifications.

First, Leri et al\(^1\) claim that we analyzed 12 pathological hearts, which is incorrect. Briefly, only 1 of the 12 studied subjects had a history of cardiac disease (a previous myocardial infarction) and was the only individual who had heart enlargement or any medication for cardiovascular disease (nitrates). Another individual died of acute myocardial infarction and displayed myocardial hypertrophy and moderate coronary sclerosis at autopsy. Of the remaining 10 individuals, 4 had slight myocardial hypertrophy, slight coronary sclerosis, and/or slight fibrosis detected at autopsy, and 1 of these had hypertension. The remaining 6 of the 12 studied individuals had neither a history of cardiovascular disease nor any sign of cardiac pathology at autopsy. Detailed information, including all of the above, was provided in our original study (Table S2), and we addressed the potential role of cardiac pathology in some of the included cases in our original publication.\(^2\)

Second, Leri et al\(^1\) claim that we assessed the birth date of a subpopulation of cardiomyocytes based on their suggestion that cardiac troponin I (cTnI) is localized in the nucleus only in a senescent subset of cardiomyocytes.\(^4\) We have addressed their claim in a separate study,\(^3\) which they fail to mention. We could not reproduce their finding using the conditions they describe in their study\(^6\) or using a range of other conditions.\(^3\) More importantly, and regardless of whether there may be a condition where one can distinguish different amounts of nuclear cTnI in cardiomyocytes, we have provided extensive characterization of the population we analyzed, which rules out that their suggestion is valid for our analysis.\(^2,3\) We identified 36.2±8.5% (mean±SD) of myocardial nuclei as cardiomyocyte nuclei, and there was no increase in the proportion of positive nuclei with age.\(^3\) This corresponds well to what one would expect if all cardiomyocyte nuclei were labeled, given that cardiomyocytes constitute 20% to 40% of the cells in the myocardium, and 25% of them are binucleated.\(^4,5\) Close to all RNA encoding the cardiomyocyte markers cTnI, cTnI, Nkx2.5, and Gata-4 is found in the cardiac troponin–positive nuclear population. Already this excludes their suggestion that we have missed a population with cytoplasmic but not nuclear cTnI, because we isolated almost all nuclei with cTnI RNA. Moreover, we independently isolated cardiomyocyte nuclei with antibodies to cTnI, which had \(^14\)C concentrations corroborating the data obtained by isolating cardiomyocyte nuclei with cTnI.\(^2\) We also demonstrated that cardiomyocytes sorted on the basis of the presence of cytoplasmic myosin heavy chain have cTnI- and cTnT-positive nuclei.\(^2\) We further established pericentriolar material 1 (PCM-1) as an additional marker to identify and isolate cardiomyocyte nuclei.\(^3\) PCM-1–positive nuclei showed an almost complete overlap with cardiac troponin–positive nuclei,\(^3\) documenting again that virtually all cardiomyocytes were \(^14\)C dated in our study.\(^2\) Thus, as we have reported previously,\(^2,3\) our findings are incompatible with their suggestion that we select for nuclei of a subpopulation of cTnI-expressing cells with a particular subcellular distribution of the protein.

Third, Leri et al\(^1\) question our interpretation of the \(^14\)C data. We used a mathematical model that is suitable for estimating cell turnover, both in slowly and fast dividing cell populations.\(^7\) This model is not limited to the assumption of a constant cell number and therefore is appropriate when analyzing tissues with a changing cell number.\(^8\) We developed 12 different scenarios for turnover based on the mathematical model, of which 2 (A and B) assumed constant renewal rates, and only 1 (A) assumed constant renewal rates and cell number. Four of 12 tested scenarios allowed the cell number and turnover rate to vary. However, this did not improve the overall fitting of the data. Leri et al\(^1\) falsely claim that we have grouped the subjects according to birth before and after the period of nuclear bomb tests. There was no grouping, and the model treats young and old subjects in the exact same way. It is, however, important to understand that \(^14\)C levels must be interpreted differently in young and old: For subjects born before 1955, \(^14\)C levels above those at the time of birth of the individual are indicative of turnover, whereas for subjects born after 1963, it is \(^14\)C levels below those at the time of birth that are indicative of cell turnover. For subjects born between 1955 and 1963 during the rapid increase in \(^14\)C levels, cell turnover can both elevate and depress \(^14\)C levels in DNA. This is accounted for in the model. Nevertheless, Leri et al\(^1\) imply that our model was erroneous because some estimated noncardiomyocyte \(^14\)C concentrations were lower than the atmospheric \(^14\)C concentrations. We agree, as stated in our initial publication, that nonmyocyte turnover estimates determined indirectly are not as robust as the cardiomyocyte turnover rate, and this will be important to address further in future studies. However, the noncardiomyocyte estimate of \(^14\)C concentrations shown in the article by Leri et al\(^1\) (Figure 8F, right panel) is incorrect. The noncardiomyocyte estimate should have a \(\Delta^{14}\)C value of 42.76 (case ND51; see Bergmann et al\(^2\)), which is above the prebomb atmospheric \(^14\)C concentration and incompatible with a \(^14\)C level of a cell population born 1000 AD.

The finding that human cardiomyocytes can be replaced throughout adulthood represents a paradigm shift in cardiovascular biology. Careful data interpretation and an appropriate mathematical analysis are required to characterize this process.

Disclosures

None.

This letter was handled by James Willerson, Consulting Editor. (Circ Res. 2012;110:e17-e18.)

© 2012 American Heart Association, Inc.

Circulation Research is available at http://circres.ahajournals.org

DOI: 10.1161/CIRCRESAHA.111.259598

e17


Cardiomyocyte Renewal in Humans
Olaf Bergmann, Sofia Zdunek, Jonas Frisén, Samuel Bernard, Henrik Druid and Stefan Jovinge

Circ Res. 2012;110:e17-e18
doi: 10.1161/CIRCRESAHA.111.259598
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/110/1/e17

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/