Cardiomyocyte Renewal in Humans

To the Editor:

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

First, Leri et al1 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 al1 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.6 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,4 which they fail to mention. We did not reproduce their finding using the conditions they describe in their study,4 which they fail to mention.

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 cTnT, 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 cTnT, which had 14C 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 14C 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 al1 question our interpretation of the 14C 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 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 14C levels must be interpreted differently in young and old: For subjects born before 1955, 14C levels above those at the time of birth of the individual are indicative of turnover, whereas for subjects born after 1963, it is 14C 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 14C levels, cell turnover can both elevate and depress 14C levels in DNA. This is accounted for in the model. Nevertheless, Leri et al imply that our model was erroneous because some estimated noncardiomyocyte 14C concentrations were lower than the atmospheric 14C 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 14C concentrations shown in the article by Leri et al (Figure 8F, right panel) is incorrect. The noncardiomyocyte estimate should have a Δ14C value of 42.76 (case ND51; see Bergmann et al), which is above the prebomb atmospheric 14C concentration and incompatible with a 14C 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.

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Olaf Bergmann, Sofia Zdunek, Jonas Frisén, Samuel Bernard, Henrik Druid and Stefan Jovinge

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