Chimera or Not Chimera?

To the Editor:

The article entitled “Evidence for Cardiomyocyte Repopulation by Extracardiac Progenitors in Transplanted Human Hearts” by Laflamme et al. published in Circulation Research, confirms our early observations that cardiac chimerism occurs after transplantation of a female heart in a male patient. These results are also in agreement with the detection of chimerism in multiple organs after bone marrow transplantation. The authors of the study in Circulation Research are perturbed by the low frequency of chimerism in their samples compared with ours (as well as in a subsequent recent report). They attribute this discrepancy to “...technical differences...” (pages 637 and 638) between the two studies. We agree completely with their assessment.

Given the resolution of the histological sections included in the article in Circulation Research, we are pleasantly surprised that they could identify even this relatively low level of chimerism. Laflamme et al place special emphasis on the stringency of their criteria for scoring Y chromosome-positive myocyte nuclei and their ability to exclude inflammatory cells in the quantitation. While we commend their thoroughness, we are surprised that they seem to doubt our ability to do the same. In fact, we believe strongly that, in addition to the better quality of histological sections, our methodology for detecting Y chromosome-positive myocytes was more stringent than theirs. One of the main reasons for using confocal microscopy is precisely to be able to unambiguously assign the nuclei to their corresponding cytoplasm. Their argument that conventional microscopy “...offers much better detection of cell borders...” (page 638) than confocal microscopy is contrary to accepted experience and disputed by the difference in resolution between their images (Figures 1–3) and ours (Figures 1, 2, and 4). Importantly, sections of 0.5 µm are analyzed by confocal microscopy while the thickness of histological sections for light microscopy is at best 5 µm. As a matter of fact, probably none of the Y chromosome-positive nuclei shown in their Figures 1 through 3 would have fulfilled our criteria to be scored as positive. This is so because of the poor definition of the boundaries of nuclei and the low intensity of the Y chromosome signal. It is also important to point out that we specifically excluded foci of inflammation in our samples. Thus, the higher level of chimerism we detected cannot be explained by selective measurement of “hot spots” (pages 634, 636, and 638).

Laflamme et al do not comment on the degree of chimerism of the vascular bed. It would have been of interest to determine whether the discrepancy in our results also extends to endothelial and smooth muscle cells given the well-established existence of blood-borne precursors of these cells responsible for producing a high level of vascular chimerism after transplant.

We believe the most likely cause for the discrepancy for the detected level of chimerism between the two studies is the difference in quality of the histological preparations and the processing of the samples. Moreover, in our view, what is important is not the quantitative differences between the two studies but their qualitative agreement. They document beyond doubt that new myocytes are generated in the adult heart from nonmyocyte precursors. The challenge now is to dissect the signaling pathways responsible for this transformation and to harness it to induce therapeutic cardiac regeneration that can be of clinical significance.

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1. Laflamme MA, Myerson D, Saffitz JE, Murry CE. Evidence for cardiomyocyte repopulation by extracardiac progenitors in transplanted human hearts. Circ Res. 2002;90:634–640; published online before print March 7, 2002. 10.1161/01.RES.0000014822.62629.EB.
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