Response to the Letter by Rose et al

We would like to reply to the letter by Drs Rose, Keating, and Backx,1 in which they gave their response to our recent publication in Circulation Research.2 In this study, we introduced alignment of transplanted stem cells as a novel determinant of functional integration of these cells with native cardiac tissue. In this study, we used neonatal rat mesenchymal stem cells (MSCs), which differentiated into functional cardiac cells after coculture with neonatal rat cardiomyocytes (CMCs). In their letter, Rose et al raise the important question of whether MSCs can differentiate into functional CMCs.1 However, we demonstrated that neonatal rat MSCs do differentiate into functional CMCs. Although we were one of the first to address the issue of cell alignment and stem cell transplantation, cardiomyogenic differentiation of MSCs derived from a premature or young organism has been shown previously by other groups.3,4 On the other hand, a number of groups, including ourselves, have shown the inability of adult MSCs to fully differentiate into CMCs.5,6 Rose et al suggest that the de novo CMCs observed in our study were not derived from MSCs but from contaminating hematopoietic stem cells. The neonatal rat MSCs used in our study contained a small fraction of CD45-positive cells, suggesting a hematopoietic origin; however, only 1.5% of the MSCs were positive for CD34, which is considered to be a key surface marker of hematopoietic stem cells. Moreover, in a study by Nishiyama et al, more than 40% of neonatal human MSCs, which were CD45-negative, differentiated into CMCs after coculture with fetal CMCs.3 However, we do agree that the issue of MSC differentiation into functional CMCs is still surrounded by uncertainties and therefore needs further study. We feel a number of aspects add to today’s confusion about stem cells and their cardiomyogenic differentiation in general. First of all, the scientific community has not yet reached consensus about a definition of a stem or progenitor cell—derived cardiomyocyte. As a result, claims are made with regard to cardiomyogenic differentiation on the basis of varied criteria and interpretations. Secondly, the way we define stem or progenitor cells affects our interpretation of scientific data, but how solid and refined are the definitions of stem or progenitor cells? In research laboratories, different methods are used to induce cardiomyogenic differentiation in stem cells, including coculture with CMCs. However, none of these methods seems to result in 100% functional differentiation. This could be attributable to the fact that the stimuli provided in a specific setting are insufficient to induce differentiation in all stem cells that are capable of cardiomyogenic differentiation. However, another possible explanation, which we favor, might be the existence of subsets of stem cells that exhibit cardiomyogenic potential, existing within a particular stem cell population (for example MSCs).7 This would imply that one cannot make a conclusion about the cardiomyogenic differentiation of MSCs as a group. To address this issue, we need more evidence for the existence of cardiomyogenic subpopulations of stem cells within larger niches. Thirdly, the limited knowledge about the mechanisms by which cardiomyogenic differentiation occurs makes it difficult to define standardized in vitro differentiation protocols. This hinders the distinction between a biological and a technical cause for the inability to induce cardiomyogenic differentiation in the candidate cells.

We acknowledge the important question that Rose et al address in their letter,1 and we encourage further discussion in the scientific community to accelerate and refine the ongoing progress in the field of stem cell–related cardiovascular research. Taken together, we feel that additional and more detailed research is needed to fully comprehend the mechanisms by which stem cell biology might offer us novel therapeutic options to treat the damaged heart but also to show us the quals and quests we need to cope with, not only today but also in the future.

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