Letter by Sluijter et al Regarding Article, “Human Cardiac Stem Cell Differentiation Is Regulated by a Mircrine Mechanism”

To the Editor:

We read with interest the article by Hosoda et al., “Human Cardiac Stem Cell Differentiation Is Regulated by a Mircrine Mechanism.” We are pleased to read that Hosoda et al. were able to confirm our observations that miR-499 is involved in the differentiation of human cardiac-derived progenitor cells.2

Hosoda and colleagues acknowledged our previous observations in human cardiomyocyte progenitor cells (hCMPCs), but claimed that these cells were erroneously considered a class of cardiac progenitor cells. The authors suggest that our results demonstrated that miR-1 and 499 favor a more mature phenotype in fetal-neonatal cardiomyocytes. Although controversy still exists about different populations of progenitor and stem cells in the heart, we used an exceptionally profound characterized and well-documented cell population,3-5 both present in the fetal and adult human myocardium. hCMPCs do express progenitor markers and early cardiomyocyte-specific transcription factors, but not any of the myofibrillar genes before their differentiation into phenotypically mature cardiomyocytes. Currently, several progenitor populations have been described that can be isolated from the heart, but no direct comparison of isolation and culture condition has been performed. This is crucial in order to understand how different these cell types really are or whether they are the product of variable isolation and culture procedures.

Performing miRNA screens with the hCMPCs,2 we observed that the myogenic miRNAs, such as miR-1, 133a, and 133b, are not expressed in our hCMPCs. These miRNAs become highly enriched, together with miR-499, on cardiac differentiation.2 Because the c-kit-positive rat cardiac stem cells used by Hosoda et al do express these miRNAs,3 there is reason to assume that these cells are already more dedicated toward the myogenic lineage than the hCMPC cell population. However, until these cells are directly compared, this is only speculative. Hosoda et al also observed that Sox6 is a direct target of the myocyte-specific miR-499; moreover, via RNAi knockdown of Sox6, that Sox6 efficiently drives cardiomyocyte differentiation.2 In addition to miR-499, miR-1 also was able to repress Sox6 expression, but we could not observe that Rcd1 is a predicted target. Hosoda et al demonstrated the enhanced myogenic potential in vitro, limited to the early cardiac transcription factors Nkx2.5 and Gata4. In addition, we did observe increased levels of cardiac actinin, Mlc-2v, and troponin T and the increased appearance of spontaneous beating areas, both in the human CMPCs and in mouse embryonic stem cells. By loading miRNA inhibitors in hCMPC, we could completely prevent their cardiomyogenic differentiation, demonstrating the prerequisite of these miRNAs for differentiation. Recapitulating, both the study by Hosoda et al and our study demonstrate independently the powerful role of miR-499 in directing the myogenic differentiation of cardiac-derived progenitor cells.

Their translational observations that miR-499 stimulated the in vivo functional differentiation of cardiac stem cells highlights the potential use of miRNAs to enhance cellular therapy, and thereby also justify the effort of mechanistic studies1-2 to understand cellular differentiation to improve regenerative therapies for the heart.

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Disclosures

None.

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References


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