Correspondence

Letter by van Mil et al Regarding, “Dynamic MicroRNA Expression Programs During Cardiac Differentiation of Human Embryonic Stem Cells: Role for miR-499”

To the Editor:

With interest, we read the recent article by Wilson et al1 in Circulation: Cardiovascular Genetics describing the role for miR-499 in dynamic microRNA (miRNA) expression programs during cardiac differentiation of human embryonic stem cells (hESCs). The authors demonstrated that a signature group of miRNAs is present in hESCs, whose expression is significantly altered after cardiomyogenic differentiation. We agree that improved understanding and selection of potential interesting miRNAs can be made.

Wilson et al investigated whether predicted targets for miR-1, -208, and -499 were reduced on cardiac differentiation in hESC. Previous studies and confirmations are needed, including other available cell sources.

In our previous study,2 we used undifferentiated human cardiode- rived progenitor cells (hCMPCs) and hCMPCs fully differentiated into cardiomyocytes (hCMPC-CM). We were pleased to read that the authors found several cardiac-related miRNAs, like miR-1, -133, -208, and -499, to be upregulated in hESC-CM (Figure 2F), which supports earlier findings showing that these miRNAs are highly upregulated in hCMPC-CM and in cardiac-differentiated ESCs.3 Moreover, miR-125, -143/-145, -199a/-214, and -27b (Figure 2D) were also highly increased in hCMPC-CM, and miR-18a, -19, -20, -25, -663, -92, and -93 (Figure 2E) were significantly decreased in hCMPC-CM. Interestingly, the embryonic-associated miRNAs (Figure 2C) were not observed in our undifferentiated hCMPCs,2 suggesting that these miRNAs are related to an ESC pluripotent state and not expressed in progenitor cells that are predestined, like the hCMPCs. We believe that by comparing different cell sources and the induction of cardiomyogenic differentiation, a more complete understanding and selection of potential interesting miRNAs can be made.

Previously, we reported the cardiac-specific expression of miR-499 and its coexpression with and location within the MYH7B gene.2 As Wilson et al.,1 we demonstrated that miR-1 and miR-499 overexpression greatly enhanced cardiomyogenic differentiation but, more importantly, that miR-1 or miR-499 inhibition could completely prevent cardiac differentiation of hCMPCs, thereby establishing the indispensable role for miR-1 and miR-499 in cardiomyogenic differentiation. Our group validated SOX6 as a target of miR-499, and by small interfering RNA inhibition of SOX6, we could greatly enhance hCMPC cardiac differentiation. Therefore, we believe that SOX6 is a crucial myogenic differentiation factor that deserves attention. In silico prediction analysis, Wilson et al confirmed that the most significant pathway targeted by miR-499 is the Wnt/β-catenin pathway, including SOX6 (Table 1). It would be interesting, therefore, to investigate whether cardiomyogenic differentiation of hESCs is governed by targeting of SOX6 as well, thereby answering important mechanistic questions about cardiac differentiation.

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Disclosures

None.

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References


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