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Cardiac progenitor-stromal cell interaction: an important player in myocardial development

Chiara Sassoli, Alessandro Pini, Sandra Zecchi-Orlandini, Daniele Bani, Lucia Formigli

Department of Anatomy, Histology, Forensic Medicine, University of Florence, Italy

There is growing support to the notion that adult mammalian heart harbours a pool of resident cardiac stem cells (CSCs). This discovery has sparked new optimism in the field of cardiac regenerative medicine based on the idea that stimulating the myocardial endogenous repair may hold greater promises than reconstituting the post-infarcted heart by transplanted exogenous stem cells. However, before considering endogenous CSCs as a target of therapeutic options in the heart failure, we need to better understand the complex mechanisms controlling heart morphogenesis, paying attention to the cellular and molecular interactions that cardiomyocyte precursors establish with other cells of the stromal compartment. On these basis, in the present study we co-cultured mouse neonatal cardiomyocytes with mouse bone marrow-derived mesenchymal stromal cells (MSCs) to investigate whether these cells could influence cardiomyocyte development in vitro. We found that proliferation of cardiac precursors was dramatically enhanced by direct co-culture with MSC as compared with the single culture system, as judged by time lapse video-microscopy and cyclin A expression/nuclear translocation. We also showed that the proliferative response of the neonatal cardiomyocytes involved the activation of Notch1 receptor by its ligand Jagged 1 and that MSCs sustained this pathway through the constitutive expression of high levels of Jagged 1. This was supported by the observations that cardiomyocytes in contact with MSCs revealed a stronger immunoreactivity for the activated Notch- intracellular domain (Notch-ICD) as compared to those in single culture. In conclusion, these findings reveal a previously unrecognized function of MSCs in regulating cardiomyocyte proliferation and development and suggest that stromal-cardiac muscle cell interactions, beside being crucial for correct myocardial morphogenesis, may represent an interesting target for innovative cell therapy strategies in cardiac regeneration.

Key words

Mesenchymal stem cell, cardiomyocyte, Notch 1/Jagged 1, co-culture