Response to Letter Regarding Article, “Growth Properties of Cardiac Stem Cells Are a Novel Biomarker of Patients’ Outcome After Coronary Bypass Surgery”

We appreciate the interest of Drs Li and Shen in our study,1 which emphasizes the critical role that the insulin-like growth factor-1 (IGF-1) and IGF-1 receptor system has in defining the growth properties of human cardiac stem cells (hCSCs). We shared their view that IGF-1 positively interferes with the consequences of diabetes mellitus and dyslipidemia, and possibly with other cardiovascular pathologies. Based on our interest in IGF-1, a transgenic mouse model with cardiomyocyte-restricted overexpression of IGF-1 was developed.2 With this strategy, an increase in the number of ventricular myocytes was obtained, resulting in a significantly lower systolic and diastolic stress at the cellular level, together with an enhanced ability of the myocardium to sustain increases in pressure or volume loads.

Overexpression of IGF-1 prevents the manifestation of the diabetic myopathy and is associated with a better survival rate of the animals,3 consistent with the observations collected in the laboratory of Drs Li and Shen. Additionally, overexpression of IGF-1 attenuates myocyte death after infarction, decreasing ventricular dilation and diastolic wall stress. Thus, IGF-1 in myocytes counteracts in vivo the death signal associated with coronary occlusion and a large segmental loss of myocardium. IGF-1, however, is unable to oppose the magnitude of myocyte death in the region of the ventricular wall supplied by the permanently occluded coronary artery.4

The protective effects of IGF-1 are not restricted to ischemic myocardial injury. Dilated cardiomyopathy in humans is characterized by scattered myocardial damage with focal areas of replacement fibrosis. Myocyte apoptosis, necrosis, and regeneration have also been implicated in this cardiac disease. However, cell death exceeds cell multiplication, contributing to the onset of heart failure. Moreover, myocyte lengthening and myofibrillar disarray participate in the depression of ventricular performance. These pathological abnormalities have been mimicked in a mouse model by overexpressing in cardiomyocytes tropomodulin, an actin filament regulatory protein.3

However, cross-breeding of tropomodulin mice with IGF-1 overexpressing mice has generated several beneficial effects on multiple indices of cardiac structure and function, including normalization of heart mass, cardiac anatomy, ventricular hemodynamics, and apoptosis.3 IGF-1 also acts as a proliferative stimulus, as evidenced by increases in myocyte number and the localization of Ki67, a nuclear marker of cell replication. IGF-1 inhibits cardiomyocyte elongation and restores calcium dynamics. These observations indicate that IGF-1 prevents partly the progression of the cardiomyopathic disease in a defined model system, and suggest that heart failure may benefit from early interventional IGF-1 treatment.

The ability of IGF-1 to interfere with the evolution of ischemic and nonischemic cardiomyopathy experimentally is consistent with the positive correlation observed in our study in humans between the circulating levels of IGF-1 and the recovery after coronary bypass surgery.1 Additionally, as in the animal models, IGF-1 appears to be a major determinant of positive and negative ventricular remodeling. Although further studies are required, the possibility is raised that circulating IGF-1 conditions the functional properties of resident hCSCs and their physiological role in the restoration of the structural and hemodynamic performance of the ischemic heart.

Disclosures

Dr Anversa is a member of Analogous, LLC. The other authors report no conflicts.

References


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Domenico D'Amario, Antonio M. Leone, Antonio Iaconelli, Nicola Luciani, Mario Gaudino, Ramaswamy Kannappan, Melissa Manchi, Anna Severino, Sang Hun Shin, Francesca Graziani, Gina Biasillo, Andrea Macchione, Costantino Smaldone, Carlo Cellini, Andrea Siracusano, Lara Ottaviani, Massimo Massetti, Polina Goichberg, Annarosa Leri, Piero Anversa and Filippo Crea

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In the article by D’Amario et al, “Response to letter regarding article, ‘Growth Properties of Cardiac Stem Cells Are a Novel Biomarker of Patients’ Outcome After Coronary Bypass Surgery’,” which appeared in the September 23, 2014, issue of the journal (Circulation. 2014;130:e118-e119. DOI: 10.1161/CIRCULATIONAHA.114.010924), a correction was needed.

Piero Anversa, MD, discloses that he is a member of Analogous, LLC.

The author regrets this omission.

This correction has been made to the current online version of the article, which is available at http://circ.ahajournals.org/content/130/13/e118.full.