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Human fetal cardiac progenitors: The role of stem cells and progenitors in the fetal and adult heart

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The human fetal heart is formed early during embryogenesis as a result of cell migrations, differentiation, and formative blood flow. It begins to beat around gestation day 22. Progenitor cells are derived from mesoderm (endocardium and myocardium), proepicardium (epicardium and coronary vessels), and neural crest (heart valves, outflow tract septation, and parasympathetic innervation). A variety of molecular disturbances in the factors regulating the specification and differentiation of these cells can cause congenital heart disease. This review explores the contribution of different cardiac progenitors to the embryonic heart development; the pathways and transcription factors guiding their expansion, migration, and functional differentiation; and the endogenous regenerative capacity of the adult heart including the plasticity of cardiomyocytes. Unfolding these mechanisms will become the basis for understanding the dynamics of specific congenital heart disease as well as a means to develop therapy for fetal as well as postnatal cardiac defects and heart failure.

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Introduction

Heart failure, most often subsequent to ischemic heart disease, is a major cause of morbidity and mortality worldwide [1]. After a large myocardial infarction, more than a billion cardiomyocytes are lost [2], and although substantial advances have been made in medical treatment improving the prognosis of these patients [3], none of the current therapeutic approaches directly targets the loss of cardiomyocytes, the underlying cause of heart failure.

For decades, the heart was viewed as a terminally differentiated organ lacking the regenerative capacity sufficient to replace the loss of myocytes following injury. The discovery of endogenous cardiac progenitor cells and reports demonstrating a low turnover of existing cardiomyocytes have changed this view to some extent [4–7]. Whether these new cardiomyocytes are derived from the proliferation of existing cardiomyocytes or from cardiac progenitor cells is still under discussion.

First-generation adult stem cell therapies, consisting mainly of bone marrow mononuclear cells, and lately even stem cell growth factor receptor (c-kit)-positive cardiac cells expanded from heart biopsies, have been studied extensively for the improvement of cardiac function after myocardial injury [8,9]. To date, however, only minor effects, if any, have been achieved through this approach [8], possibly attributed to paracrine mechanisms without the evidence of replacement for lost cardiomyocytes [10].

Second-generation therapies use alternative strategies, based on molecular pathways and transcription factors guiding cardiac differentiation, to regenerate the myocardium by delivering lineage-specified cardiopoietic mesenchymal stromal cells, transplanting cardiomyocytes derived from embryonic stem (ES) cells, or directly converting heart fibroblasts into cardiomyocytes by inducing core cardiac transcription factors [11–15].

The third generation of cardiac stem cell therapies is needed to increase the pool of cardiomyocytes to the level that prevents or reverses the negative remodeling of the myocardium leading to heart failure. This future approach should be based on a deeper understanding of cardiogenesis, and it should aim to enhance the heart's intrinsic regenerative capacity through the activation of endogenous progenitor cells or the stimulation of cell cycle reentry and expansion of adult cardiomyocytes.

On the other side of the cardiovascular disease spectrum, there are the congenital heart defects characterized by structural abnormalities of the heart or the great vessels or functional abnormalities in electrical conduction. Although rare diseases, these are often life threatening for the fetus or the young patient, and it is therefore imperative to try to develop new therapies for these defects. Congenital heart diseases are viewed mainly to be consequences of mutations in the transcriptional pathways that regulate heart development [16–18]. Thus, recent progress in uncovering the intrinsic signaling pathways important for directing the fate of the multipotent cardiac progenitors (canonical Wnt signaling, insulin growth factor (IGF), Notch, and Hippo signaling) might yield clinically relevant information that could be used to prevent and correct fetal heart malformations and for regenerating the adult human heart.

This review will highlight the contribution of different cardiac progenitors to the embryonic heart development, the endogenous regenerative capacity of the adult heart including the plasticity of cardiomyocytes, as well as the linkage between cardiac progenitors and congenital heart disease, and how cardiac progenitors might be able to contribute to heart regeneration after myocardial injury.

Cardiac development

The heart is one of the first organs to be developed during embryogenesis and the first organ that displays function. The heart is derived from the mesodermal germ layer, which is specified into the cardiac mesoderm through the interaction of inductive and inhibitory signals from the adjacent endoderm and ectoderm. These signals include wingles integrated (Wnt), fibroblast growth factor (FGF), and transforming growth factor-β (TGF-β) pathways leading to the activation of early cardiomyocyte transcriptional programs [19–24]. The next step in cardiogenesis is the specification and differentiation of these cells through the development of specific heart fields [18,23]. The first, or primary, heart field (FHF) forms the cardiac crescent in the anterior splanchnic mesoderm at