Healthy and Unhealthy Cardiac Progenitor Cells Modify the Pathogenesis of Myocardial Diseases

Andrey Kazakov, Ulrich Laufs

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a life-threatening inherited cardiomyopathy with an estimated prevalence of 1 per 5000 individuals characterized by the replacement of the cardiac myocytes with fibrofatty tissue leading to ventricular arrhythmias, right ventricular failure, and sudden cardiac death.\(^1\) ARVD/C is commonly inherited in an autosomal dominant manner with an incomplete penetrance and variable expressivity caused by mutations in desmosomal genes (eg, plakoglobin, plakophilin-2, desmoplakin, desmoglein-2, and desmocollin-2) and several nondesmosomal genes (such as ryanodine receptor, phospholamban, transmembrane protein 43, titin, and TGFβ3).\(^2\)

FAPs are present in healthy muscular tissue. They rapidly enter the cell cycle in response to acute muscle injury but do not generate myofibers. FAP along with the satellite cells participate in muscle regeneration providing a source of cytokines that regulate satellite cell activity and establishing an environment enhancing myogenic differentiation.\(^4\) However, under pathological conditions, FAPs may impair muscle structure and function. Uezumi et al\(^5\) described a population of fibro-adipogenic progenitors (FAPs) in the skeletal muscle that express platelet-derived growth factor receptor-α (PDGFRA). FAPs are present in healthy muscular tissue. They rapidly enter the cell cycle in response to acute muscle injury but do not generate myofibers. FAP along with the satellite cells participate in muscle regeneration providing a source of cytokines that regulate satellite cell activity and establishing an environment enhancing myogenic differentiation.\(^4\) However, under pathological conditions, FAPs may impair muscle structure and function. Uezumi et al\(^5\) described a population of fibro-adipogenic progenitors (FAPs) in the skeletal muscle that express platelet-derived growth factor receptor-α (PDGFRA).

In this issue of Circulation Research, Lombardi et al\(^6\) highlighted the importance of mutated stem cells and stem cells with disturbed differentiation capacity for the pathogenesis of cardiovascular diseases. The pivotal role of mutated stem cells for pathological processes is known. For example, mutations in resident tissue stem cells can transform them into cancer stem cells initiating tumor growth.\(^7\) The number of cancer-related gene mutations in resident tissue stem cells increases with age.\(^8\) Several distinct stem cell populations have been described in the adult heart, including ISL1\(^+\) cells, epicardium-derived cells, KIT\(^+\) cells, SCA1\(^+\) cells, and PDGFR\(α\)^+ cells, as well as cardiospheres and side population cells.\(^9\) Although most investigations report a protective role of resident and bone marrow–derived stem cells in the myocardium by improving regeneration, angiogenesis, and cardiac fibrosis,\(^10\) stem cells play not only a beneficial role in cardiovascular diseases (Figure). Cardiovascular risk factors impair regenerative capacity of stem and progenitor cells deteriorating cardiovascular cell turnover and favoring the progression of heart failure. The bone marrow–derived endothelial progenitor cells demonstrate an impaired migratory function in patients with coronary artery disease, which inversely correlated with the number of risk factors and revealed increased oxidative DNA damage, decreased telomerase activity, and decreased telomere length.\(^11\) Aging reduces the number and function of endothelial progenitor cells and resident cardiac stem cells.\(^11,12\) Particularly, in the cohort of patients that represents the most likely candidates for regenerative...
therapy, >50% of their resident cardiac stem cells can be senescent with reduced regenerative capacity. These cells show short telomeres and increased apoptosis. Senescence, cardiovascular risk factors, and pathological conditions can redirect the differentiation of resident and bone marrow–derived stem cells toward a fibrotic phenotype. In the adult heart, cardiac fibroblast turnover is low. However, under pathological conditions, such as cardiac hypertrophy or myocardial infarction, cardiac fibroblast can originate from the circulating bone marrow–derived stem cells that can differentiate toward fibroblasts or fibrocytes. For example, both pressure overload or inhibition of endothelial nitric oxide synthase causes mobilization of fibrocytes from the bone marrow and increases their number in the myocardium. On the contrary, interventions such as lipid-lowering or physical exercise improve progenitor cell function and thereby improve cardiovascular health.

The study of Lombardi et al demonstrates that unhealthy stem cells contribute to cardiac fibrogenesis and participate in the pathogenesis of inherited heart diseases. By crossing of PDGFRA+/EGFP mice with the Myh6-Cre:DspW/W mouse model of ARVD/C, the authors show that the mutation of desmoplakin in FAPs causes the formation of fibrofatty tissue leading to ARVD/C. An interesting finding of the fat-mapping experiment is the expression of PDGFRA locus by >20% cardiomyocytes during cardiac development. In the murine embryo, PDGFRA is expressed in the early mesoderm, including cardiac mesoderm and in cardiac neural crest directing the differentiation, migration, and function of stem and progenitor cells during embryonic organogenesis. Moreover, PDGFRA-deficient mice show defects of the outflow tract and septal, chamber, and coronary vessels. The heterogeneous expression of PDGFRA in cardiomyocytes may reflect their distinct origin from the different types of stem and progenitor cells during embryonic development. These studies set the stage for further investigations that are needed to elucidate the role of developmental heterogeneity of cardiac myocytes in healthy and diseased hearts.

In conclusion, the work of Lombardi et al identifies a novel disease mechanism, namely, the pivotal role of the desmoplakin gene deletion in the human and mouse cardiac FAP cells for the fibrofatty tissue formation leading to arrhythmogenic right ventricular dysplasia/cardiomyopathy. This elegant study thereby highlights the important contribution of unhealthy stem cells in the pathogenesis of cardiovascular diseases.

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References


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