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

Andrey Kazakov, Ulrich Laufs

A rrhythmogenic 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. 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).1

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From the Klinik für Innere Medizin III Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätsklinikum des Saarlandes Homburg, Saarland, Germany.

Correspondence to Ulrich Laufs, Klinik für Innere Medizin III Kardiologie, Angiologie und Internistische Intensivmedizin, IMEG Geb. 41.1, Universitätsklinikum des Saarlandes 66421 Homburg, Saarland, Germany. E-mail ulrich.laufs@uks.eu

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Present in the myocardium and participate in the pathogenesis of ARVD/C. The authors sorted cardiac cells from human and mouse hearts to isolate PDGFRA+ cells and excluded cells expressing other lineage and fibroblast markers. The PDGFRA+ Lin'THY1'DDR2' cells expressing desmosome proteins from mouse and human hearts were identified as FAPs. The majority expressed the fibroblast marker collagen 1A1 and a subset expressed the adipogenic transcription factor CCAAT/enhancer-binding protein α. The FAPs expressed desmosome proteins including desmoplakin, predominantly in the adipogenic but not in their fibrogenic subsets. Conditional heterozygous deletion of desmoplakin in mice using a Pdgfra-Cre deleter led to increased myocardial fibro-adipogenesis and suppressed the canonical wingless-related integration site (Wnt) pathway. Genetic fate–mapping experiments demonstrated an origin of ≈40% of adipocytes in the fibrofatty tissue from the progenitor cells. The activation of the Wnt signaling reduced adipogenesis and normalized transcript levels of adipogenic genes. This elegant study demonstrates the presence of the PDGFRA+ FAPs in the adult mammalian heart and the importance of the desmplakin gene mutation in these progenitor cells for the replacement of the myocardium with the fibrofatty tissue.

The work of Lombardi et al6 highlights 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. The number of cancer-related gene mutations in resident tissue stem cells increases with age. Several distinct stem cell populations have been described in the adult heart, including ISL1+ cells, epicardium-derived cells, KIT+ cells, SCA1+ cells, and PDGFRe+ cells, as well as cardiospheres and side population cells. 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, 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. Aging reduces the number and function of endothelial progenitor cells and resident cardiac stem cells. 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.11 These cells show short telomeres and increased apoptosis.12 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.12 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.13 For example, both pressure overload or marrow–derived stem cells that can differentiate toward fibrocytes. ISL-1 indicates insulin gene enhancer protein 1; KIT, stem cell growth factor receptor or tyrosine-protein kinase Kit (CD117); PDGFRA, platelet-derived growth factor receptor-α; and SCA1, stem cell antigen-1.

The study of Lombardi et al6 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;Dsp/WF 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.6 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.9 The heterogeneous expression of PDGFRA in cardiomyocytes may reflect their distinct origin from the different types of stem and progenitor cells during embryonic development.9 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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