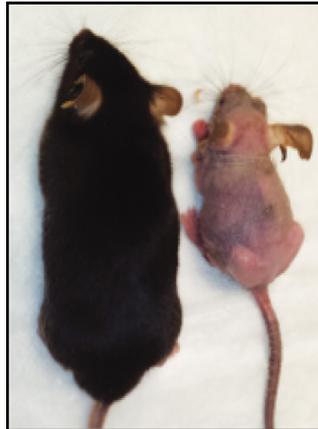


**T3+Dex Generates Functional T-Tubules in hiPSC-CM (p 1323)**

**Parikh et al develop a protocol for promoting t-tubule formation in human iPSC-derived cardiomyocytes.**

Cardiac myocytes derived from human induced pluripotent stem cells (hiPSC-CMs) are useful for modeling a variety of heart diseases and potentially for repairing injured hearts. But the process of in vitro hiPSC-CM differentiation generally fails to produce fully mature cells. For example, they tend to lack t-tubules—membranous invaginations that transverse the cell and are essential for normal cellular electrophysiology. Previous strategies for improving hiPSC-CM maturation include growing the cells on a matrix of physiological stiffness (matrigel mattress) and adding thyroid and glucocorticoid hormones to the media. However, neither of these approaches promote fully fledged t-tubule development. Parikh and colleagues have now discovered that by combining these two approaches, the iPSC-CMs could be made to develop t-tubules that are morphologically and functionally mature, ie, they display synchronized intracellular calcium release and improved excitation-contraction coupling. The new maturation approach could not only improve the production of mature cardiac myocytes for disease modeling and clinical use, say the authors, but also provide a useful tool for unravelling the molecular mechanisms of t-tubule development.



**Cellular Basis of Cardiocutaneous Syndromes (p 1346)**

**Karmouch et al identify the cellular basis of cardiocutaneous syndrome, and create a mouse model of the disease in the process.**

Arrhythmogenic cardiomyopathy (ACM) is characterized by ventricle arrhythmias that occur prior to cardiac dysfunction. Some patients experience palpitations, fainting, even sudden death, before any chronic heart defect is apparent. The condition is most commonly caused by mutations in desmosomes, which are cell-to-cell adhesion proteins. Homozygous mutations in the desmosomal proteins desmoplakin or plakoglobin, for example, cause cardiocutaneous syndrome, a form of ACM, in which patients have skin and hair abnormalities (including alopecia) in addition to arrhythmia. Karmouch and colleagues have identified a distinct subset of cells associated with cardiocutaneous syndrome. They found that cells expressing Cspg4 (chondroitin sulfate proteoglycan 4) are present in the skin and cardiac conduction system—and that conditional deletion of desmoplakin in Cspg4-positive cells in mice recapitulated the human symptoms of cardiocutaneous syndrome—namely arrhythmia prior to cardiac dysfunction and alopecia. This new model should aid investigations into the molecular mechanisms of the syndrome and potentially, identification of relevant therapeutic targets.

**Thyroid Function and Atherosclerotic Outcomes (p 1392)**

**Increased thyroid activity may increase a person’s risk of atherosclerosis, say Bano et al.**

High thyroid activity has been linked to hypertension, hypercoagulation, and atrial fibrillation, whereas low thyroid activity has been linked to hyperlipidemia and inflammation. In principle, either situation could contribute to atherogenesis, but investigations into the relationship between thyroid activity and the formation of atherosclerotic lesions have given mixed results. Some studies report an increased risk with higher thyroid function, while other reports associate atherogenesis with lower thyroid function. Some studies have reported no link at all. To resolve the issue, Bano and colleagues carried out a large-scale clinical study in which 9420 subjects were followed for an average of 9 years. The study encompassed the full spectrum of atherosclerosis—from subclinical artery calcification to adverse cardiovascular events and death. They found that high levels of free thyroxine—an indicator of high thyroid activity—was associated with increased artery calcification, as well as with a higher risk of adverse events and death. The association remained significant even in the absence of other cardiovascular risk factors—such as body mass index and lipid levels—and within ranges of thyroid activity considered normal. The authors conclude that thyroxine could be a useful marker for identifying atherosclerosis patients most at risk of morbidity and mortality.

# Circulation Research

JOURNAL OF THE AMERICAN HEART ASSOCIATION



## In This Issue Ruth Williams

*Circ Res.* 2017;121:1291

doi: 10.1161/RES.000000000000187

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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