Too much plakoglobin protein in the nuclei of heart cells turns them into fat cells and causes arrhythmia, report Lombardi et al.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is most commonly caused by mutations to genes encoding desmosome proteins, such as plakoglobin (PG). ARVC-causing mutations in PG are known to release the protein from intercellular junctions and drive its accumulation in the nucleus where it suppresses canonical Wnt signaling. To determine whether nuclear accumulation was essential for the pathogenesis of ARVC, Lombardi and colleagues made transgenic mice that overexpressed mutant or wild-type PG in the heart. They found that both proteins accumulated in the nucleus (exclusively, in the case of mutant PG), that the mice suffered arrhythmias, and that their hearts contained large numbers of fat cells (adipocytes)—a characteristic feature of ARVC. Indeed, cardiac progenitor cells isolated from the mice could spontaneously develop into adipocytes in culture. These cells also showed suppression of Wnt signaling. Treating the cells with a drug called BIO restored Wnt signaling and reversed the proadipogenic phenotype. Although the results might not be applicable to other causes of ARVC, they do suggest that those cases caused by mutant PG might benefit from a heart-directed reactivation of canonical Wnt signaling.

Wnt Signaling Regulates CSP Cells (p 1363)

Wnt signaling inhibits cardiac progenitor cell proliferation and reduces the ability of heart to repair, say Oikonomopoulos et al.

Progenitor cells in the adult heart are activated after injury and help to regenerate the tissue. Little is known about the mechanisms that regulate progenitor cell renewal, however. Oikonomopoulos and colleagues wondered whether the signaling protein Wnt might be involved, because it has been shown that Wnt promotes the proliferation of neonatal and embryonic cardiac progenitors in vitro and in vivo. Wnt can affect the development and differentiation of tissues in different ways, depending on the type of tissue and the stage of development. For example, early in embryo development, Wnt activates cardiac differentiation, but later, it becomes inhibitory. Sure enough, the team found that unlike in embryonic and neonatal progenitors, Wnt signaling in adult progenitors inhibited proliferation—both in the culture dish and when injected into mouse hearts. Wnt signaling led to a 40-fold increase in expression of the growth factor binding protein, IGFBP3, and in the absence of Wnt signals, overexpression of IGFBP3 could mimic the effect of Wnt signaling. The authors say that inhibiting Wnt or IGFBP3 might, therefore, be an effective approach for improving tissue regeneration after cardiac injury.

Plasmacytoid Dendritic Cells and Atherosclerosis (p 1387)

Plasmacytoid dendritic cells keep atherosclerotic inflammation in check, report Daissormont et al.

Plasmacytoid dendritic cells (PDCs) make up a tiny percentage of total leukocytes and are a small but consistent presence in atherosclerotic plaques. In vitro studies suggest that PDCs might contribute to the pathogenesis of atherosclerosis, particularly to the destabilization of plaques—a dangerous precursor to blood vessel occlusion. However, their role in atherosclerosis in vivo has not been established. Until now, that is. Daissormont et al depleted PDCs in a mouse model of atherosclerosis and showed that plaque volumes increased and that they contained greater numbers of T cells. The number of T cells was also increased in the blood and spleen. Together, these data suggested that PDCs suppress T-cell proliferation—which the team confirmed in vitro—and that this suppression occurred throughout the body, not only in plaques. PDCs isolated from atherosclerotic mice expressed higher levels of the immunomodulatory factor IDO. Furthermore, in cocultures of PDCs and T cells, IDO inhibition increased the proliferation of T cells, showing that PDC suppression of T-cell proliferation is IDO dependent. This suggests that boosting PDC/IDO activity might be a new therapeutic strategy in the fight against atherosclerosis.
In This Issue

Circ Res. 2011;109:1319
doi: 10.1161/RES.0b013e318241d3a2
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/109/12/1319

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/