CD40L-Mac-1 and Atherosclerosis (p 1269)

Wolf et al have devised a safer way to block CD40L in atherosclerosis. CD40L is a cell surface glycoprotein that is expressed on a variety of cell types and that interacts with several cell surface receptors. One of its main roles is to regulate lymphocyte function, and therefore, it is involved in a number of inflammatory diseases, including atherosclerosis. Blocking the action of CD40L reduces the formation and growth of atherosclerotic plaques and lowers their lipid and monocyte content. Despite these beneficial effects, clinical trials with anti-CD40L have identified some dangerous side effects, such as the risk of thromboembolism and impaired host immunity. Wolf et al have now designed a specific peptide that blocks the interaction of CD40L with the receptor Mac-1, which is found on leukocytes, but that leaves interactions with other receptors intact. Blocking this interaction in a mouse model of atherosclerosis reduced leukocyte recruitment to plaques and attenuated plaque growth. Importantly, the peptide did not affect thrombus formation—thought to be mediated via the interaction of CD40L with a platelet receptor—nor did it alter the basic immunological characteristics of these mice. The investigators suggest that targeted disruption of the CD40L-Mac-1 interaction may be a better strategy for treating atherosclerosis than the general inhibition of CD40L.

Epigenetic Control of Endothelial Lineage (p 1219)

Endothelial progenitor cells require epigenetic remodeling to switch on endothelial genes, say Ohtani et al. Endothelial progenitors are necessary for vascular repair and neovascularization after ischemia, but little is known about the mechanisms controlling the differentiation of these progenitor cells into functional endothelial cells. Ohtani et al found that in endothelial progenitors the promoter regions of a number of endothelial-specific genes were tagged with epigenetic marks of silencing—DNA and histone methylation. However, when the endothelial progenitor cells were exposed to hypoxic conditions, these marks of silencing were removed and replaced with marks of active chromatin—histone acetylation. Hypoxic tissue is known to be a fertile ground for recruiting endothelial progenitors for neovascularization. The team found that pharmacological inhibition of the enzymes that methylate histones and that remove histone acetyl groups could activate the endothelium-specific gene, eNOS. Endothelial progenitor cells, particularly those expressing eNOS, have been shown to improve functional recovery after ischemia in animal models. Understanding how endothelial progenitor cells differentiate and switch on their essential genes could thus help in improving clinical approaches to ischemic injury repair.

Spontaneous Termination of Human VF (p 1309)

Blocking potassium channels in diseased hearts could avert potentially fatal fibrillations, report Farid et al. Ventricular fibrillation—the rapid uncoordinated contraction of ventricle muscle—is the most common cause of sudden cardiac death in humans. Often, the only way to stop ventricular fibrillation is with an electric shock. Consequently, patients with severe cardiomyopathy who are at risk of ventricular fibrillation are generally treated using implantable defibrillator devices, which deliver tiny electric jolts to the heart when arrhythmias are detected. Farid et al have now found evidence to suggest that an alternative or adjunctive therapy might be possible. Myopathic human hearts showed increased expression of ATP-dependent potassium channels in their left ventricular endocardiums compared with those of normal hearts. This aberrant expression was thought to be the cause of the electrical instability. Importantly, blocking potassium channel activity with a drug called glibenclamide could induce spontaneous termination of ventricular fibrillation. In addition to use in cardiomyopathy patients K-ATP channel blockade by glibenclamide might prove useful in patients that need defibrillation after cardiac surgery or those that require cardiopulmonary resuscitation, say the authors.
In This Issue

Circ Res. 2011;109:1195
doi: 10.1161/RES.0b013e31823da8e2
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/109/11/1195

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/