

Cholesterol's link to heart disease gets clearer -- and more complicated

February 2 2010

By considering molecular-level events on a broader scale, researchers now have a clearer, if more complicated, picture of how one class of immune cells goes wrong when loaded with cholesterol. The findings reported in the February 3rd issue of *Cell Metabolism* show that, when it comes to the development of atherosclerosis and heart disease, it's not about any one bad actor -- it's about a network gone awry.

The new findings also highlight a pretty remarkable thing, Heinecke says: "Despite 30 years of study, we still don't know how cholesterol causes heart disease." But, with the new findings, scientists are getting closer.

Earlier studies had shown that heart disease is about more than just high LDL ("bad") cholesterol. Cells known as macrophages also play a critical role. Macrophages are part of the innate immune system that typically gobble up pathogens and clear away dead cells. But they also take up and degrade cholesterol derivatives. When they get overloaded with those lipoproteins, they take on a foamy appearance under the microscope to become what scientists aptly refer to as foam cells. Those foam cells are the ones that seem to have critical importance in the development of atherosclerosis.

People had typically thought about this problem in terms of linear pathways, Heinecke explained. In essence, macrophages end up with too much cholesterol going in and not enough coming out. The macrophages get overwhelmed and trapped in the artery wall, and somehow plaques

form as a result.

But the new results show that it isn't really about simple paths in and out; rather, there is an integrated network of macrophage proteins involved. When that network gets disrupted, as it does when too much cholesterol comes in, atherosclerosis forms. "It's definitely a different way to think about what is going on," Heinecke says.

Heinecke's group applied sophisticated technologies and statistical tools to get a global view of what happens to macrophage proteins when they turn into foam cells. Their analysis revealed what they call a macrophage sterol-responsive network (MSRN), including proteins already known to work together. Most of them are also found in one place, within microvesicles outside the macrophage cells.

The researchers further found that drugs used to lower cholesterol and inflammation, including statins and rosiglitazone, restore the macrophage network to almost normal, even in mice that don't have the LDL receptors that are considered the usual targets of the drugs. On the other hand, mice lacking single proteins in the network, including APOE and so-called complement proteins of the immune system, have macrophages that look like foam cells even when they aren't loaded with cholesterol.

The findings suggest that anything that sends the macrophage network off kilter could promote heart disease, Heinecke said. They also change the way researchers should think about how [heart disease](#) is treated. The key may be how to best restore the function of an integrated network rather than to lower [cholesterol](#) levels or ratchet individual proteins up or down.

"We propose that the atherogenic actions of cholesterol-loaded [macrophages](#) are an emergent property that results when the normal

balance of MSRN proteins in microvesicles is perturbed," the researchers conclude. "We further suggest that certain dietary factors or genetic variations can disturb this network, thereby promoting vascular disease. By integrating mouse and human data, we hope to better understand the MSRN's role in foam cell formation, with the long-term goal of identifying therapeutic interventions for targeting networks rather than individual proteins."

Provided by Cell Press

Citation: Cholesterol's link to heart disease gets clearer -- and more complicated (2010, February 2) retrieved 26 April 2024 from <https://medicalxpress.com/news/2010-02-cholesterol-link-heart-disease-clearer.html>

<p>This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.</p>
--