MedicalXpress

The long arm of the dendritic cell: A link between atherosclerosis and autoimmunity

April 4 2012

Patients with autoimmune diseases often show a predisposition to develop "hardening of the arteries" or atherosclerosis. LMU researchers have now uncovered a mechanism that establishes a causal link between the two disorders.

Individuals who suffer from autoimmune diseases also display a tendency to develop atherosclerosis – the condition popularly known as hardening of the arteries. Clinical researchers at LMU, in collaboration with colleagues in Würzburg, have now discovered a mechanism which helps to explain the connection between the two types of disorder. The link is provided by a specific class of immune cells called plasmacytoid dendritic cells (pDCs). pDCs respond to DNA released from damaged and dying cells by secreting interferon proteins which stimulate the immune reactions that underlie autoimmune diseases. The new study shows that stimulation of pDCs by a specific DNA-protein complex contributes to the progression of atherosclerosis. The findings may have implications for new strategies for the treatment of a whole spectrum of conditions that are associated with chronic inflammatory reactions.

Atherosclerosis is a major cause of death in Western societies. The illness is due to the formation of insoluble deposits called atherosclerotic plaques on the walls of major arteries as a consequence of chronic, localized inflammation reactions. By reducing blood flow, the plaques can provoke heart attacks and strokes. A class of immune cells called dendritic cells plays a crucial role in facilitating the development of these plaques. The term refers to a heterogeneous cell population that

makes up part of the immune system. Among the cell types represented in this population are the so-called plasmacytoid dendritic cells (pDC), but their potential significance for atherosclerosis had not been explored until now. A group of researchers led by Dr. Yvonne Döring in Professor Christian Weber's department at LMU, together with a team supervised by Privatdozentin Dr. Alma Zernecke of Würzburg University, has now shown how pDCs promote the development of atherosclerosis - and explained why patients with autoimmune disorders, such as psoriasis or systemic lupus erythematodes (SLE), show a predisposition to atherosclerosis.

Using laboratory mice as an experimental model, the researchers were able to show that pDCs contribute to early steps in the formation of atherosclerotic lesions in the blood vessels. Stimulation of pDCs causes them to secrete large amounts of interferons, proteins that strongly stimulate inflammatory processes. The protein that induces the release of interferons is produced by immune cells that accumulate specifically at sites of inflammation, and mice that are unable to produce this protein also have fewer plaques. Stimulation of pDCs in turn leads to an increase in the numbers of macrophages present in plaques. Macrophages normally act as a clean-up crew, removing cell debris and fatty deposits by ingesting and degrading them. However, they can also "overindulge", taking up more fat than they can digest. When this happens, they turn into so-called foam cells that promote rather than combat atherosclerosis. In addition, activated, mature pDCs can initiate an immune response against certain molecules found in atherosclerotic lesions, which further exacerbates the whole process.

The stimulation of pDCs provides the link between atherosclerosis and autoimmune diseases. "The pDCs themselves are stimulated by the self-antigens that set off the autoimmune reactions which result in conditions like psoriasis and SLE," says Döring. Indeed, it is well known that the secretion of interferons by activated pDCs contributes to the genesis of a

number of autoimmune diseases

"The newly discovered involvement of pDCs in the development of atherosclerosis establishes a direct link between this disorder and autoimmune reactions, and reveals why the stimulation of pDC that is characteristic of autoimmune diseases contributes to the progression of atherosclerosis," says Weber. "The findings also suggest new approaches to the treatment of chronic inflammation that could be useful for a whole range of diseases."

More information: Auto-Antigenic Protein-DNA Complexes Stimulate Plasmacytoid Dendritic Cells to Promote Atherosclerosis, Y. Döring, H. Manthey, M. Drechsler, D. Lievens, R. Megens, O. Soehnlein, M. Busch, M. Manca, R. R. Koenen, J. Pelisek, M. J. Daemen, E. Lutgens, M. Zenke, C. J. Binder, C. Weber, A. Zernecke, *Circulation*, published online March 2, 2012. circ.ahajournals.org/content/e … LATIONAHA.111.046755

Provided by Ludwig-Maximilians-Universität München