BRUNO BUCHHOLZ

## The inhibition of a surface receptor delays the progression of atherosclerosis

Haddad Y, Lahoute C, Clément M, Laurans L, Metghalchi S, Zeboudj L, et al. The dendritic cell receptor DNGR-1 promotes the development of atherosclerosis in mice. **Circ Res 2017;121:234-43. http://doi.org/cbbw**

Histological studies of advanced atherosclerotic lesions demonstrate the presence of large necrotic and acellular areas. Cellular death in the atheromatous plaque may occur as a result of lytic lesions of oncotic characteristics, with large cellular and organelle edemas, rupture of the plasma membrane and subsequent release of its intracellular content, or as a consequence of apoptosis. The accumulation of apoptotic cells and remains of necrotic tissue in the lipid nucleus is an important cause of the progression of atherosclerotic lesions and is associated with a strong increase in the risk of thrombotic complications as a result of plaque rupture. This accumulation leads to a pro-inflammatory immune activation that accelerates the progression of arterial disease.

Cell death by apoptosis may be beneficial or deleterious depending on the cell type involved and the stage of plaque evolution. When it occurs in late stages, release of substances into the extracellular environment exposes tissues to toxic enzymes, oxidative substances and others such as proteases and caspases. An endogenous way of counteracting this progression of atherosclerosis is removal through phagocytosis of dead cells or in the process of dying, thereby reducing damage to the surrounding tissue. This phagocytosis is mainly mediated by macrophages and dendritic cells, and is a specialized process that allows the elimination of apoptotic cells before the loss of membrane permeability. Although the role of phagocytosis in limiting the progression of atherosclerosis is well known, the molecular relationship of necrosis and disease development has not been fully studied.

In the present study, Haddad et al. used an experimental model of transgenic mice lacking the dendritic cell NK lectin group receptor-1 (DNGR-1) and with hypercholesterolemia due to apolipoprotein e deficiency (ApoE−/−). ApoE mice spontaneously develop hypercholesterolemia and atheromatous plaques, being a widely used model for the study of atherosclerosis. On the other hand, DNGR-1 receptors are preferentially expressed in macrophages and some subtypes of dendritic cells and are involved in the detection of apoptotic and necrotic cells of the lipidic nucleus. The authors observed that, in the context of moderate hypercholesterolemia, the absence of the DNGR-1 receptor decreases the vascular inflammatory response, with a lower T lymphocyte and macrophage infiltrate and a reduction in plaque size. These transgenic mice have a higher expression of the anti-inflammatory cytokine IL-10, which is the main mechanism of action. Contrary to this, the genetic inhibition of IL-10 expression abolished the protective effect of DNGR-1 absence.

*It is well known that an unstable plaque has high lipid content, with a large nucleus of dead cells and a thin fibrous layer which makes it susceptible to easy rupture, and that all this response has as common denominator a very high inflammatory activity. The existence of a cell-surface receptor (DNGR-1) with strong pro-inflammatory and pro-atherogenic properties makes it a potential study target, as its blockade could stabilize atherosclerotic plaques and delay their evolution.*