Inhibiting a single protein could improve the treatment of atherosclerosis

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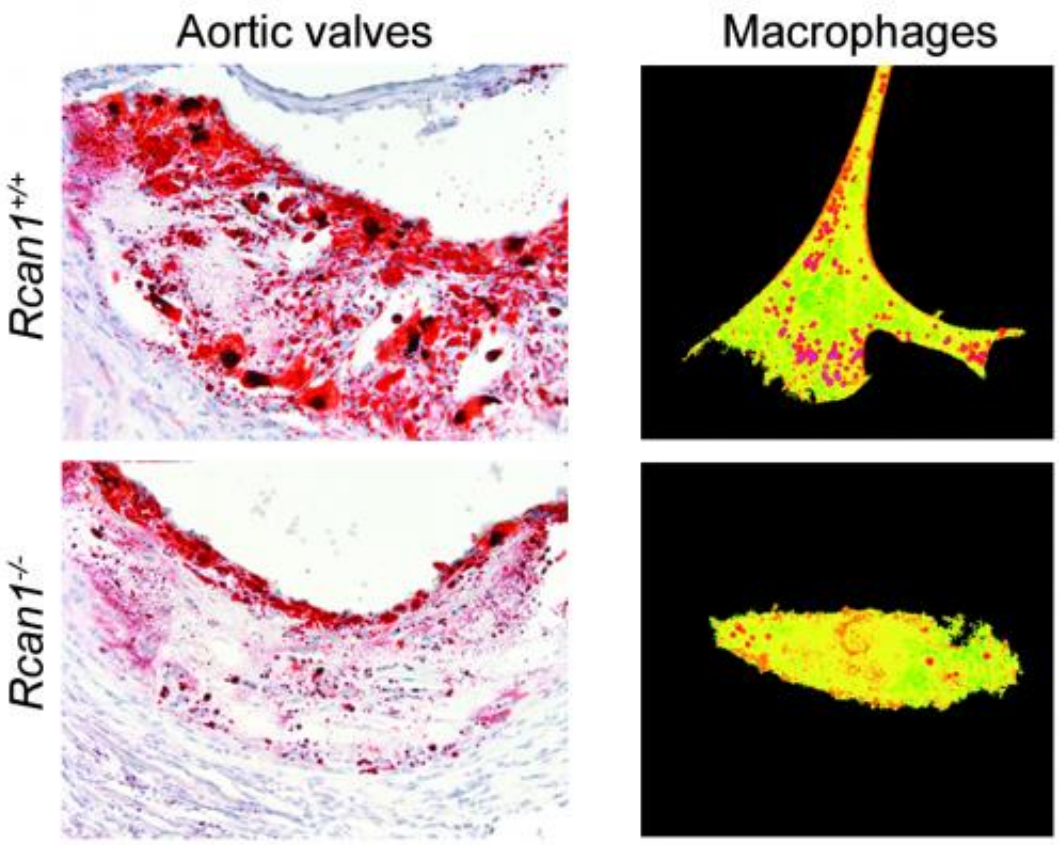

Rcan1 genetic inactivation reduces LDL cholesterol accumulation (red staining) in aortic valves and macrophages, the most important inflammatory cells in the atherosclerotic plaque. Credit: CNIC / CSIC

Researchers of the Spanish research council (Consejo Superior de Investigaciones Científicas, CSIC) and the Centro Nacional de

Investigaciones Cardiovasculares (CNIC) have discovered that inhibiting the protein Rcan1 in mice reduces the burden of atherosclerosis, one of the commonest cardiovascular diseases. The results of their study, published in the prestigious journal *EMBO Molecular Medicine*, suggest that Rcan1 is a potential target for future drug treatments for this disease, and the team is already working to develop this potential.

The study analyzed the molecular mechanisms involved in the formation and progression of atherosclerotic plaques in mice fed a diet high in fat and cholesterol. As first author Nerea Méndez, of the CNIC, explains, "It was already well-known that this diet increases the risk of atherosclerosis, but the new study shows that it does this by increasing the expression of the protein Rcan1".

Dr. Miguel Campanero, researcher at the Instituto de Investigaciones Biomédicas Alberto Sols and joint lead author of the study together with Dr. Juan Miguel Redondo of the CNIC, continues, "We found that not only is the expression of Rcan1 much higher in atherosclerotic arteries, but also that genetic inactivation of this protein represses the development of the disease by favoring the appearance of anti-inflammatory characteristics in macrophages and reducing their accumulation in plaques."

Atherosclerosis is a very common disease worldwide and is linked to common features of the modern lifestyle, especially inappropriate diet and physical inactivity. The disease arises when deposits of LDL cholesterol—also known as 'bad cholesterol'—and other fats form plaques in the wall of arteries. This triggers the activation and recruitment of monocytes, a type of white blood cell, which transform into macrophages and engulf the cholesterol particles.

This seemingly positive action in fact stimulates the recruitment of additional inflammatory cells and favors the deposition of more

cholesterol. Over time, the affected artery accumulates not only fats but also calcium, which hardens the plaque and narrows the artery, restricting the bloodflow. These hardened plaques are unstable and vulnerable to rupture, which produces internal hemorrhages leading to the formation of blood clots within the arteries. If these clots obstruct the blood vessel, the result can be a heart attack or stroke.

It is therefore very important to identify ways to slow the progression atherosclerosis, but available treatments are associated with undesired side effects of varying severity. The findings published in *EMBO Molecular Medicine* are therefore very welcome news.

Dr. Redondo says "the development of more effective treatments depends, in general, on the identification of proteins whose expression or function is altered specifically in the target cells. To do this, we need to understand the molecular mechanisms involved in the development of each disease."

Dr. Campanero adds that the results of the study "suggest that the use of procedures to inhibit the expression or function of Rcan1 could be more effective and specific than current treatments for reducing atherosclerosis."

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