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Study shows why cholesterol damages arteries

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The presence of crystalline cholesterol in the walls of our arteries is a major cause of life-threatening inflammation. This has been demonstrated in a study jointly run by the universities of Massachusetts, Bonn and Munich. The potential consequences include heart attack, stroke or sudden cardiac death. The researchers' results will be published in the next edition of the scientific journal *Nature*.

In addition to crystallized cholesterol, atherosclerotic plaques always contain large quantities of immune cells but, surprisingly, no bacteria or viruses. It was previously unclear just how the body's own defence forces are called into action. Even animals that are kept in an absolutely sterile environment can suffer from "clogging" or "furring" of the arteries when their food contains high levels of cholesterol. The same relationship is found in humans. The higher the blood cholesterol level, the greater the risk of atherosclerosis and the greater the likelihood of suffering a heart attack. "We have known this for a long time", points out Professor Dr. Eicke Latz from Bonn University, "but nobody understood exactly why".

Professor Latz has been exploring this question in collaboration with Dr Peter Düwell from LMU Munich, Professor Veit Hornung, also from Bonn University, and research colleagues based in the US. The researchers have succeeded for the first time in identifying the molecular trigger for inflammation in large blood vessels. "We've found that, given a certain type of nutrition, cholesterol crystals are deposited in the arterial walls after a relatively short time", says Dr Düwell. "These

crystals are then taken up by the immune system's scavenger cells". This becomes the starting signal for a catastrophic chain reaction. The unhealthy food results in the accumulation of cholesterol crystals that activate an "inflammasome" complex within the scavenger cells. One of the functions of this multi-protein complex is to induce the release of inflammatory mediators. The mediators then attract more and more immune cells to the site where the problem is occurring. The growing invasion ultimately destabilizes the vessel walls - with potentially life-threatening consequences.

Gout in the arteries

"Very similar processes are observed with cases of gout", explains Professor Latz, "although that mainly occurs in the joints". Extremely painful attacks of gout can also be triggered by an unhealthy diet. This time however, the culprit is not fat but nucleic acids from, for instance, muscle tissue (meat). The uric acid formed in the digestion process then crystallizes. These crystals can unleash a powerful inflammatory reaction.

Professor Latz has recently been recruited by the University of Bonn after working ten years in basic research in the United States. Here, he heads the new Institute for Innate Immunity (Institut für Angeborene Immunität), which has a research focus on the immune mechanisms that cause inflammatory reactions. The innate immune system forms part of the body's own defence mechanism and is able to respond rapidly and directly to a number of alarm signals that appear in the tissue environment. These triggers not only include viruses, bacteria and fungi but also certain crystals and other substances that occur during infections of in stress situations. The strength of the innate immune system is that it can respond very quickly to situations that are of danger to the host. The problem, however, is that it can also overshoot the mark. This type of overreaction is also seen in the case of pneumoconioses such as the black

lung, a disease which frequently affects miners. In these lung diseases, a chronic inflammatory reaction is triggered by inhaled crystals made of silicates or asbestos. The molecular mechanisms of crystal recognition are similar to those triggered by cholesterol crystals in blood vessels.

Starting point for developing new drugs

There is still a piece of the jigsaw puzzle missing which researchers need to complete the overall picture. "We don't know precisely how the cholesterol crystals activate the inflammasome", says Professor Latz. The findings of this study however, offer some starting points for developing new drug therapies. At present, statins are widely used in therapy. Statins reduce the synthesis of endogenous - i.e. the body's self-produced cholesterol and diminish the risk of heart attack or stroke, but they cannot inhibit the absorption of cholesterol from ones diet.

Estimates by the World Health Organization put the number of people now dying from cardiovascular diseases at almost 17 million per year. This means that one in four deaths worldwide is caused by atherosclerosis.

Provided by University of Bonn