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Scientists identify cholesterol-regulating genes

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Scientists at the European Molecular Biology Laboratory (EMBL) and the University of Heidelberg, Germany, have come a step closer to understanding how cholesterol levels are regulated. In a study published today in the journal *Cell Metabolism*, the researchers identified 20 genes that are involved in this process. Besides giving scientists a better idea of where to look to uncover the mechanisms that ensure cholesterol balance is maintained, the discovery could lead to new treatments for cholesterol-related diseases.

"This finding may open new avenues for designing targeted therapies, for example by looking for small molecules that could impact these genes," says Heiko Runz, whose group at the University Clinic Heidelberg carried out the research together with Rainer Pepperkok's lab at EMBL.

High levels of cholesterol in the bloodstream are a major risk factor for atherosclerosis and coronary heart disease, one of the leading causes of death in developed countries today. Nevertheless, cholesterol is an important cellular component: 90% of the cholesterol in our bodies is inside our cells, where it does not cause any harm. Blood cholesterol levels are partly regulated by cells taking up cholesterol from the bloodstream, a process Runz and his colleagues are helping to unveil.

The researchers deprived isolated human cells of cholesterol and then looked at the whole genome to find the genes that react to changes in cholesterol levels by altering their expression. This large-scale approach

pointed to hundreds of genes which might be involved in cholesterol regulation. To check which genes really were involved, the scientists used a technique called RNA interference to systematically turn each of the candidate genes off. With a microscope they then observed what effect switching off different genes had, both on cholesterol uptake and on the total amount of cholesterol inside cells.

Of the 20 genes the scientists identified as involved in regulating cholesterol levels and uptake, 12 were previously unknown. The remainder were known to have some link to lipid metabolism - how the body breaks down fat - including two genes that when mutated may cause heart disease, but which were only now shown to also play a part in bringing cholesterol into cells in the first place.

The scientists are now trying to discover exactly how the novel genes regulate cholesterol levels inside cells, as well as looking at patients to determine whether these genes (or alterations in them) do constitute risk factors, and investigating if and how they could be useful drug targets.

This discovery could help fight not only heart disease, but also other conditions, as one of the genes identified appears to influence the behaviour of NPC1, a protein involved in the neuro-degenerative Niemann-Pick disease.

The research was conducted under the Molecular Medicine Partnership Unit (MMPU), a collaboration between EMBL and Heidelberg University. "It is very convenient to have such a close partnership here in Heidelberg", says Rainer Pepperkok from EMBL, adding, "it allowed us to use the sophisticated techniques and technology from EMBL to answer questions that first arose at the University clinic, whose clinical aspects will now help in the follow-up."

Source: European Molecular Biology Laboratory (news : web)