Newly discovered gene regulates balance of 'bad' cholesterol

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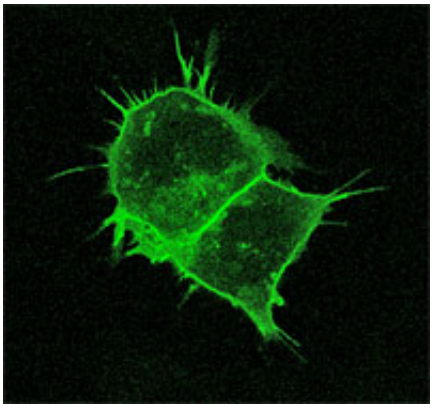

IDOL

In an article in *Science*, Noam Zelcer from the LACDR (The Netherlands) describes a previously unknown mechanism for regulating the amount of LDL cholesterol. This offers opportunities for supplementing and improving the effect of so-called statins: medicines that remove 'bad' cholesterol from the bloodstream.

Cholesterol is not water-soluble. In order to be transported in the blood, it therefore forms fat globules, called lipoproteins, together with other fats. The two most familiar are known as HDL (high density lipoprotein) or ‘good’ cholesterol, and LDL (low density lipoprotein) or ‘bad' cholesterol. Too much LDL in the blood can contribute to the development of cardiovascular diseases.

A group of substances, known as statins, is often used as a medication to reduce the LDL level in the blood. They achieve this by on the one hand blocking the production of cholesterol and on the other hand by raising the number of receptors for LDL on the cells of the liver. This allows the cells to absorb more LDL from the blood, so that the blood becomes 'cleaner'. Statins are currently the most frequently sold medicines. However, they are not perfect.

The development of statins is based on the cell's natural mechanisms for regulating the cholesterol balance. All cells have the ability to make, absorb or excrete cholesterol. And all cells have to treat cholesterol with care: too much cholesterol in the cell is toxic, but too little is also not good. Cholesterol is needed for such purposes as forming membranes. Cells can 'sense' the amount of cholesterol and regulate the level by pumping it away if there is too much. If they want to obtain cholesterol from outside, they raise the level of the LDL receptor. This receptor binds to 'free ranging' LDL and absorbs it into the cell, where the fat globule is broken down into its different components, including cholesterol itself.

Noam Zelcer, now part of the Leiden/Amsterdam Center for Drug Research (LACDR), together with Peter Tontonoz and other former colleagues at the University of California in Los Angeles, has discovered a previously unknown mechanism that explains how cells regulate cholesterol levels. On the website of the journal *Science* (*Science Express* 11 June), he describes a mechanism that influences the number of LDL receptors.

If active IDOL is present in the cell, the number and positioning of the LDL receptors alters dramatically.

Zelcer identified a gene that influences the breakdown of these receptors. 'The gene works like a traffic controller,' he explains. 'As soon

as there is too much cholesterol in the cell, it sends the LDL receptors to the lysosome, the waste processing centre of the cell. They are broken down there, so that the cell absorbs less cholesterol and the balance is restored.'

Zelcer named the cell IDOL, which stands for Inducible Degrader Of the LDLR. This cell repairs the internal balance. But the same degradation mechanism that maintains the internal balance could well be a factor that prevents statins from working optimally: namely allowing LDL to be removed from the blood by cells. Zelcer: 'There are indications that this could be the case, so we have studied what happens if we switch off the IDOL.' Raised receptor level They managed to do this successfully, both in mice cells and in human cells in a test tube. As soon as the researchers inactived the IDOL, or reduced the amount, the level of the LDL receptor rose, so that the cell was able to absorb more LDL cholesterol. Zelcer is now researching wh ether influencing IDOL might lead to a new cholesterol-reducing therapy that complements the working of statins.

Source: Universiteit Leiden