'Death receptors'—New markers for type 2 diabetes and cardiovascular disease

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Researchers at Lund University in Sweden have found that the presence of death receptors in the blood can be used to directly measure the risk of developing cardiovascular diseases and type 2 diabetes. "We see that people with known risk factors such as high blood sugar and high blood fats also have heightened death receptor levels," says Professor Jan Nilsson who led the study.

Death receptors are activated in the case of infections when white blood cells that have combatted a virus are to be removed. It was previously known that death receptors in the blood can be measured, but not whether an elevated level was linked to increased cell death in type 2 diabetes and arteriosclerosis.

The aim of the study was therefore to investigate whether "death receptors" could be used as a marker to establish ongoing tissue damage and if this could be used to predict the risk of developing cardiovascular diseases and type 2 diabetes. The results show that increased cell death can be linked to increased levels in the blood of three different members of the same "death receptor family" (TNFR-1, TRAILR-2 and Fas). Increased cell death is seen in type 2 diabetes and arteriosclerosis.

High blood sugar and blood fats—low levels of HDL, "the good cholesterol"—subject the body's blood vessels and insulin-producing beta cells to stress. Long-term stress damages the cells and can cause the death receptors on the surface of the cell to trigger a cell suicide program within the cell.

"When the beta cells are damaged, the production of insulin decreases, which increases the risk of diabetes. The damage activates repair processes in blood vessels. If these are not properly resolved, this usually leads to the development of plaque in the blood vessels (arteriosclerosis). The formation of cracks in this plaque is the primary cause of myocardial infarction and stroke," says Jan Nilsson.

The study also looked at the connections between different risk factors—age, BMI, blood fats, blood sugar and blood pressure—and the death receptors TNFR-1, TRAILR-2 and Fas in blood samples from 4742 people who are part of the population study Malmö Diet Cancer.

Samples from the 1990s were compared with the risk of suffering from diabetes, heart attack and stroke in the coming 20 years.

The results show clear links between the level of death receptors in the blood and the different risk factors. High levels of death receptors were common in diabetics, which indicates increased cell stress and risk of damage to different organs. Among non-diabetics, high levels of death receptors were linked with an increased risk of developing diabetes and cardiovascular diseases. This indicates that the level of death receptors in the blood reflects the damage that the risk factors cause in different organs.

"On the other hand, we could not see that the level of death receptors is linked to the risk of developing cardiovascular disease among diabetics, which is a paradox. We don't yet really understand why, but it could be the case that the level of the biomarkers, i.e. death receptors, among diabetics is already very high," says Jan Nilsson.

The conclusion is that the presence of death receptors in the blood could be used as a measurement of ongoing tissue damage and to predict the risk of developing type 2 diabetes and cardiovascular disease.

"This indicates that we could at an early stage get an idea of whether treatment of risk factors reduces damage to beta cells and blood vessel walls by monitoring the death receptors in the blood," says Jan Nilsson.

"We hope that the markers can be used in future clinical studies or in the development of new drugs," says Ingrid Yao Mattisson, a doctoral student who has been very active in conducting the study.

More information: Ingrid Yao Mattisson et al. Elevated Markers of Death Receptor-Activated Apoptosis are Associated with Increased Risk for Development of Diabetes and Cardiovascular Disease, *EBioMedicine* (2017). DOI: 10.1016/j.ebiom.2017.11.023

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