Molecular switch controls the destiny of self-eating cells

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The study is the result of a collaboration of scientists at Karolinska Institutet in Sweden, University of Michigan, and University of California San Diego, USA, who were interested in finding out whether autophagy can be affected by events in the cell nucleus. Surprisingly, they discovered that a signal chain in the nucleus serves as a kind of molecular switch that determines whether the cell dies or survives.

Put simply autophagy is a process whereby the cell consumes parts of itself, and is a way for it to clean up abnormal lumps of proteins and rid itself of damaged organelles (the cell's 'organs') by breaking them down. The cell also uses the process when stressed by external circumstances, such as starvation, to keep itself alive until better times. So while autophagy can protect the cell, it can also lead to its death. However, just how the choice between life and death is controlled has remained a mystery.

Autophagy is involved in numerous diseases, such as cancer, diabetes, obesity, cardiovascular disease, chronic inflammations, Alzheimer's and Parkinson's diseases, as well as in physiological adaptation to exercise, the development of the immune system and ageing.

"Given the role of autophagy in human disease, all we have to do is select a disease model and test whether there's anything to be gained from influencing the new signal network that we've identified," says Dr Bertrand Joseph at Karolinska Institutet's Department of Oncology-Pathology, who headed the study.

To date, autophagy has mainly been considered a process in the cell's cytoplasm; the present study can completely overturn this view since the results indicate that events in the cell nucleus play an essential part in controlling the process once it has started. The DNA in the cell nucleus is packed around so-called histone proteins, on which different enzymes can attach acetyl groups. Such histone modification is a type of epigenetic regulation, which can influence gene expression without changing the DNA sequence. The modification of histones is a dynamic process, since some enzymes add the acetyl groups and other enzymes remove them.

The researchers studied how the outcome of the autophagy was affected by the acetylation of histone H4, and found that during the processes the acetylation of H4 decreased, which led to a reduction in the expression of autophagy-related genes. If this specific histone modification was blocked, the autophagic cells died.

"Our findings open up avenues for influencing autophagy," says Dr Joseph.

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