Old Cells Work Differently

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The agglutination and accumulation of proteins in nerve cells are major hallmarks of age-related neurodegenerative illnesses such as Alzheimer's disease. Cellular survival thus depends on a controlled removal of excessive protein. Scientists at Johannes Gutenberg University Mainz (Germany) have now discovered exactly how specific control proteins regulate protein breakdown during the ageing process.

Every protein in our cells has a defined life span. At the end of this time and even sooner (e.g., in response to injury caused by external factors such as oxidative stress), proteins are eliminated by means of a specific protein degradation process. The quantity of proteins requiring elimination can rise in the face of ongoing oxidative stress, as can occur during the ageing process and in neurodegenerative illnesses. Damaged proteins that cannot be rendered harmless through the cell's "protein purification plant" tend to aggregate and accumulate, thereby threatening the survival of the cell. Nerve cells are especially susceptible to such protein accumulation, and the agglutination of proteins in nerve cells is a characteristic pathological symptom of a wide spectrum of age-associated neurodegenerative illnesses in humans, such as Alzheimer's disease and Parkinson's disease. Effective protein quality control is thus a requirement for the survival of all cells.

It has already been postulated for some time that it is specifically this quality control mechanism that changes with the cellular ageing process, but it is only now that Professor Christian Behl's team at the Institute of Pathobiochemistry of Mainz University has succeeded in finding the critical molecular proof. They were able to precisely identify the

proteins that on the molecular level regulate both of the potential cellular pathways for protein degradation - the proteasome and the lysosome pathways. The scientists were able to show how the control function of these proteins changes during the cell's ageing process.

These new discoveries, principally based on doctoral research by Martin Gamerdinger, are of the greatest importance for understanding the pathogenesis of age-associated neurodegenerative illnesses, and were prominently published in the EMBO Journal on 19 February. "We will only be able to discover and investigate the precise causes of age-associated neurodegenerative illnesses such as Alzheimer's disease and develop causal therapies if we closely consider the molecular changes that take place as nerve cells age. Alzheimer's is one of the diseases typically associated with old age; it has its origin and progresses in old nerve cells," emphasizes Christian Behl, confirming the importance of Gamerdinger's findings.

Collaborators in the research project were Professor Uwe Wolfrum of the Institute of Zoology of Johannes Gutenberg University Mainz and Professor Ulrich Hartl of the Max Planck Institute of Biochemistry in Martinsried near Munich. They focused their research on defining the special role of the proteins BAG1 and BAG3 in protein degradation during the ageing process. They were able to demonstrate that BAG1 and BAG 3 regulate the proteasomal and lysosomal protein elimination pathways, respectively. "It is interesting that there is a switch from BAG1 to BAG3 that accompanies the cellular ageing process, and this change results in increased activation of the lysosomal protein breakdown pathway- the so-called ‘macroautophagy' pathway," explains first author Martin Gamerdinger. He started by studying human fibroblasts, and then successfully reproduced his findings in nerve cells.

A similar BAG3-mediated, considerably more potent macroautophagy pathway also becomes predominant in the ageing rodent brain; the

authors postulate that this change may be a way of compensating for the increased load of damaged proteins in older cells. The dysfunction of this molecular switch as individuals age may be the reason for the malfunction of the cellular "protein purification plant" and account for the subsequent accumulation of proteins in nerve cells, as occurs in human neurodegenerative diseases. This will be investigated in more detail in future studies using specific disease models.

More information: Protein quality control during ageing involves recruitment of the macroautophagy pathway by BAG3, Martin Gamerdinger, Parvana Hajieva, A. Murat Kaya, Uwe Wolfrum, F. Ulrich Hartl & Christian Behl
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