OF BRAINS, HOLES, AND MITOCHONDRIA...

Mitochondria are rod-shaped organelles, roughly the size of bacteria, found in the cytoplasm of nearly all cells. Despite their tiny size, however, mitochondria can pack a mighty punch; they are the powerhouses of the cell, harnessing energy from the oxidation of food molecules in the form of adenosine triphosphate (ATP).

Healthy mitochondria are especially critical for the proper functioning of specialised cells of the brain and spinal cord, called neurons. When mitochondria fail, neurons die. That is why Professor Neville Vassallo, at the Department of Physiology and Biochemistry and the Centre for Molecular Medicine of the University of Malta, believes that mitochondria might hold the key to understanding the molecular underpinnings of brain neurodegenerative disorders.

Two of the most common neurodegenerative diseases are Alzheimer's disease (AD) and Parkinson's disease (PD), which afflict millions of people around the world. AD causes a progressive and relentless loss of memory and, ultimately, identity of the individual. In PD the impairment is primarily motor, featuring a tremor at rest, slowness or even absence of voluntary movement, and a festinating gait.

"AD and PD were first characterised pathologically by Dr Alois Alzheimer (1864-1915) and Dr Friedrich H. Lewy (1885-1950) respectively, at the Psychiatric Clinic of the University of Munich in the early 1900s," Prof. Vassallo explains.

Prof. Neville Vassallo

When these eminent neuropathologists peered down their microscopes to look at histological sections obtained from brain autopsies of their patients, they saw abundant plaque deposits and widespread degeneration of neurons. Since then, the search has been on to understand exactly how neurons might be killed by the toxic clumps (also known as oligomers) of protein deposits. "Answering this basic question," says Prof. Vassallo, "will be essential for development of effective, potentially disease-modifying therapies for these devastating diseases."

Several years of intensive research along an often tortuous investigative pathway by Prof. Vassallo and his collaborator Dr Ruben Cauchi and their teams, have resulted in the recent publication of two key papers that may shed new mechanistic insights into the neuronal degenerative process. Perhaps not surprisingly, mitochondria lie at the heart of this mechanism. Prof. Vassallo and his co-workers have discovered an intriguing process that occurs when healthy mitochondria organelles are exposed to toxic oligomeric structures of α-synuclein and tau proteins, which form the deposits in the brains of individuals with AD or PD.

Essentially, oligomeric clusters of α-synuclein and tau proteins drill nano-sized holes in the lipid membrane envelope of mitochondria, and since the mitochondrial membrane is the site where generation of ATP occurs, the poration of mitochondria leads to a bioenergetic crisis of the neuron, the outcome of which is ultimately cell death.

In their research papers, the UM scientists have observed several indicators of mitochondrial damage, including swelling of mitochondria and release of death-signalling molecules such as cytochrome c. Furthermore, using highly sensitive electrophysiological equipment, they actually measured the disruptive currents created by the anomalous flow of ions through the nanopores in the mitochondria.

Interestingly, these latest research findings tie in nicely with earlier work from Prof. Vassallo's laboratory, showing that the membrane-activity of α-synuclein and tau oligomers is linked to the presence of cardiolipin, a signature phospholipid of mitochondrial membranes that plays a central role in mitochondrial bioenergetics.

A direct implication of these studies is that mitochondrial damage may potentially be inhibited by developing small-molecule compounds that are able to prevent toxic α-synuclein and tau clusters from forming pores in mitochondria, hence ensuring survival of the neuron.

Indeed, in close collaboration with research groups at the German Centre for Neurodegenerative Disease Research in Munich, Germany, and the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany, Prof. Vassallo and his group succeeded in attenuating mitochondrial damage using a potent anti-aggregator molecule called 'anle138b'. Patented by the German biotech company Modag GmbH, anle138b is currently in clinical trials as a potential treatment for Parkinson's disease. Prof. Vassallo hence underscores the importance of fundamental research in developing effective cures for AD and PD: "It is only by knowing the fundamentals that one can develop effective therapeutic strategies to treat patients. Our aim is to keep alive the hope of those suffering from neurodegenerative diseases, and their families, for a better cure."

Members of Prof. Vassallo's research team who have worked on this project include Dr Angelique Camilleri, Dr Stephanie Ghio, and Dr Mario Caruana. ■

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