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De-stressing of the Endoplasmic Reticulum by ER-phagy Prevents Neurodegeneration

Abstract

The longest nerve cells in our bodies—some stretching from the spinal cord to the toes—are also the most vulnerable. These long extensions (called axons) carry signals that allow us to move, feel, and interact with the world. But their extraordinary length may also be their greatest weakness, making them especially prone to degeneration in certain inherited diseases.

In our research, we identified several genes linked to rare hereditary disorders that damage these long nerve fibers. Surprisingly, many of these genes are responsible for shaping a vast and dynamic structure inside cells called the endoplasmic reticulum (ER). The ER acts as a cellular factory and storage center: it helps build proteins and carefully regulates calcium, a crucial signaling molecule.

When the proteins that maintain the ER's shape are defective, the ER becomes distorted and stressed. This stress leaves nerve cells more vulnerable to self-destruction. One key player is a protein called FAM134B. It serves as a quality-control manager by initiating the degradation of damaged portions of the ER, a specialized recycling process known as ER-phagy. By clearing out defective ER fragments, this process helps restore balance inside the cell.

When ER-phagy fails, damaged components accumulate, stress increases, and neurons begin to degenerate. Beyond the nervous system, this recycling pathway is also essential for removing misfolded proteins and maintaining quality control in other cell types.

Our findings highlight how the health of the cell's internal architecture is vital for the survival of long nerve fibers — and how subtle disruptions in cellular recycling can ultimately lead to neurodegenerative disease.

CV

Prof. Dr. med. Christian A. Hübner is Full Professor (W3) and Director of the Institute of Human Genetics at Jena University Hospital and the Medical Faculty of Friedrich Schiller University Jena. After studying medicine at Medizinische Hochschule Hannover and the University of Alabama completing clinical and postdoctoral training in Heidelberg and Hamburg, he specialized in Human Genetics and obtained his habilitation in Neurobiology. Since 2010, he has led the Institute of Human Genetics in Jena. Prof. Hübner is an internationally recognized expert in human genetics and neurobiology, actively contributing to academic leadership as Vice President of the German Society of Human Genetics and Vice Dean for Research of the medical faculty. He has been awarded several scientific awards. He has extensive experience in teaching and mentoring, having supervised numerous doctoral and postdoctoral researchers and supported several early-career scientists in achieving international tenure positions.