Mitochondria are important parts of cells that provide energy and keep the cell functioning properly. They also support various processes, like producing essential molecules needed for life, including heme (important for blood), nucleotides (building blocks for DNA), amino acids, fatty acids, and cholesterol. Mitochondria are very flexible and can quickly adapt to changes in the cell. Most of the proteins needed for mitochondria are encoded in the cell's nucleus and synthesized outside this organelle, which means that mitochondrial proteins have to be brought into the mitochondria. This process is carried out by special protein transporters found in the two membranes that surround the mitochondria. It means that their activity can influence the speed of the protein translocation and thus overall function of mitochondria. However, we do not fully understand how this transport process is regulated at the level of these protein transporters.

The membranes of mitochondria are mostly made of lipids, which are types of fat molecules. Some of these lipids play a role in the process of energy production by modulating the proteins involved in this process. However, it is unclear how lipids affect the transport of proteins into the mitochondria. Recently, we discovered that a protein called TIMM17A, which is involved in protein transport into the mitochondria, controls the levels of a lipid called phosphatidylethanolamine (PE) by regulating the enzyme (PISD) that synthesizes it in the inner membrane of the mitochondria.

In cells, most PE is made in the mitochondria, and then delivered to other parts of the cell. This suggests that by controlling the enzyme that makes PE, cells can regulate the amount of this lipid in the mitochondria, potentially impacting mitochondrial function. This discovery could provide insight into how the cell maintains its balance and how certain diseases, including mitochondrial disorders, are linked to problems with lipid metabolism.

People with certain genetic mutations in the gene responsible for making PE (PISD) develop mitochondrial diseases because their cells do not produce sufficient amounts of this important lipid. However, how the body adapts when PE levels are low is still unclear. Our research shows that cells with low PE levels have more special fat (triglycerides), suggesting that the body tries to compensate for this shortage.

The goals of this project are to study how PE levels are controlled in human cells, understand how PISD and thus PE affect mitochondrial function, and identify how cells adjust to shortage of PE. We will use various laboratory methods as well as advanced techniques like transcriptomics (studying gene expression), proteomics (studying proteins), and lipidomics (studying fats), to investigate these processes.

What is the significance of this study?

Mitochondria are crucial for health, and their malfunction is linked to diseases like neurodegenerative disorders, diabetes, and cancer. This research could uncover a new way that that human cells control the protein load in the mitochondrial membrane, which is directly connected to mitochondrial function. Such universal processes are often hijacked by viruses and diseases like cancer. In fact, cancer cells often increase mitochondrial function, so targeting these processes could help develop treatments to slow tumor growth. Overall, this research could improve our understanding of how problems with mitochondrial function lead to diseases, helping to create better diagnosis and treatment options.