Lipid droplets are structures found in various cell types across many organisms, including humans. They store excess lipids—cholesteryl esters and triacylglycerols—within the cell. Serving as an energy reservoir, these droplets can be utilized by the cell during periods of increased metabolic demand. By storing excess fat, lipid droplets protect the cell from lipotoxicity, which can lead to cell death. Disruptions in the biogenesis and function of lipid droplets are associated with numerous diseases.

In cancer cells, lipid droplets play a particularly important role. They provide energy and participate in adaptive processes, including the development of resistance to chemotherapy. Lipid droplets also form contacts with other organelles, such as **mitochondria**, which act as the cell's primary energy producers.

Current treatment strategies for cutaneous melanoma involve combinations of drugs targeting two major signaling pathways that are frequently deregulated during tumorigenesis. Unfortunately, such therapies can lead to metabolic adaptation in cancer cells, potentially resulting in drug resistance.

The distribution and function of lipid droplets and mitochondria depend, among other factors, on the actin cytoskeleton. Actin is involved in many cellular processes, including cell motility, organelle transport, adhesion, shape maintenance, and cell division. It exists in monomeric (G-actin) and filamentous (F-actin) forms, and its polymerization is regulated by proteins such as formins. One such formin is **FHOD1**, which polymerizes actin and crosslinks F-actin filaments, leading to the formation of thick actin bundles. This influences cell shape and motility. FHOD1 is expressed in various cancers, including cutaneous melanoma.

In our research, we observed that FHOD1 localizes around lipid droplets in different types of cancer cells. We identified the region of the protein responsible for this localization. Preliminary results indicate that reducing FHOD1 levels leads to a decrease in the number of lipid droplets and alters their intracellular distribution. We also found FHOD1 at contact sites between lipid droplets and mitochondria. Lowering FHOD1 levels results in changes in mitochondrial morphology and distribution, as well as increased energy production, suggesting the induction of mitochondrial stress.

Based on these findings, we propose that FHOD1 is involved in the organization, distribution, and function of lipid droplets and mitochondria, thereby influencing the metabolism of melanoma cells.

To test this hypothesis, we plan to conduct a series of experiments. After generating FHOD1 knockout cells, we will examine how the absence of this protein affects lipid droplet formation, distribution, and interaction with mitochondria. We will also assess whether reduced FHOD1 levels influence mitochondrial metabolism and the sensitivity of melanoma cells to currently used therapies. As part of this project, we will collaborate with Prof. Andrew Wilde from the University of Toronto (Canada), who will help identify molecular partners of FHOD1 on the surface of lipid droplets and mitochondria. Additionally, we will perform animal studies (in mice) to determine whether the combined deletion of FHOD1 and administration of melanoma therapies yields better outcomes than chemotherapy alone.

Our research will employ state-of-the-art techniques, including high-throughput automated cell imaging and cellular metabolism analysis.

Understanding the role of FHOD1 in the formation, organization, and function of lipid droplets and mitochondria will deepen our knowledge of how the actin cytoskeleton influences these structures and cellular metabolism. In the future, this may contribute to the development of new therapeutic strategies for treating not only cancer but also metabolic diseases.