

## Lay summary

Cell growth is very much like building a house, which requires all kind of building materials in sufficient amounts. Overseeing the construction is the building manager, a protein known as mTORC1. For example, when mTORC1 detects that there isn't enough of a building material such as amino acids, it will stop construction until new amino acids become available. The coordination between availability of nutrients and initiation of cell growth is crucial for maintaining functional cells and tissues. When mTORC1 becomes dysfunctional and loses its ability to coordinate these two processes, numerous metabolic diseases can result.

In our lab we recently discovered that mTORC1 oversees an important building material, cholesterol. Cholesterol is an essential component of cellular membranes, and is also a precursor for hormones and other bioactive molecules. One organelle, the lysosome, is the main sorting station where cholesterol derived from the diet is delivered to other compartments within the cell for utilization. The lysosome is also the site within the cell where mTORC1 becomes activated. Interestingly, we discovered that mTORC1 is exquisitely sensitive to the cholesterol content of the lysosome, and that altering cholesterol trafficking has major consequences for the ability of mTORC1 to regulate downstream processes.

These findings may have important implications for the pathogenesis of a cholesterol storage disorder known as Niemann-Pick type C. This disease is caused by the loss of the NPC1 protein, and is characterized by the accumulation of cholesterol inside the lysosome. It is believed that the pathology of this disease is caused by the over-accumulation of cholesterol, which decreases the functionality of the lysosome thus reducing cell fitness. However, our findings suggest that mTORC1 dysregulation may be a previously unrecognized driver in the progression of Niemann Pick type C. This notion positions our lab in a unique position to shed new light on the mechanisms of Niemann-Pick disease pathogenesis.

This research proposal is aimed first at investigating growth signaling in cells derived from Niemann-Pick patients. We will quantify the activity of key growth pathways by systematically measuring metabolite changes that occur as a consequence of NPC1 loss, and we will identify a 'metabolic signature' that distinguishes patient cell from healthy ones. Because mTORC1 activity affects these cellular pathways, we will next use genetic and pharmacological approaches to manipulate mTORC1 activity and revert the metabolic behavior of Niemann-Pick cells toward a healthy state.

We believe that our investigations of mTORC1 biology will allow us to look at Niemann-Pick disease as more than a lysosomal storage disorder, and may contribute to the design of novel therapeutic approaches.