

Final report Ofer Moldavski - Lay summary

Cell growth is akin to building a house, which requires all kinds of building materials in sufficient amounts. Overseeing the construction is the 'cellular building manager', a protein kinase known as mTORC1. mTORC1 constantly monitors the available cellular building materials, such as amino acids, lipids and sugars, and regulates the rate of the growth process accordingly. The coordination between availability of nutrients and the initiation and rate 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 diseases can result, including cancer, type-2 diabetes and various age-related conditions.

In our lab we recently discovered that mTORC1 oversees an important cell-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 growth processes.

These findings prompted us to investigate how a cholesterol storage disorder known as Niemann-Pick type C impacts mTORC1 activity. 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 overall cell fitness. Our findings show that in the absence of the NPC1 protein, mTORC1 becomes hyperactive and is virtually insensitive to cholesterol levels. Thus, we hypothesize that aberrant mTORC1 activation may be a previously unrecognized driver in the progression of Niemann Pick type C. This notion places our lab in an ideal position to shed new light on the mechanisms of Niemann-Pick disease pathogenesis.

As mTORC1 drives lipid synthesis, whereas NPC1 promotes cholesterol trafficking, the newly found link between mTORC1 and NPC1 implies that proper coordination of their activities is essential for normal cholesterol metabolism. However, whether and how mTORC1 and NPC1 are co-regulated is unknown. Cholesterol derivatives known as oxysterols are potent regulators of sterol metabolism. An intuitive question that arise is from our discoveries is whether oxysterols can regulate lipid biosynthesis via mTORC1 and NPC1. To address these questions we screened a group of oxysterols and tested their ability to regulate the activities of mTORC1 and NPC1. This screen led us to the identification of the oxysterol, 4-Hydroxycholesterol (4-HC), which can activate mTORC1 specifically while inhibiting NPC1 function through alteration of its subcellular localization . Additionally, we discovered that 4-HC is unique among oxysterols due to its ability to drive the synthesis and accumulation of another lipid class, fatty acids.

Because mammalian blood contains elevated levels of 4-HC, our findings suggest that 4-HC may be an important regulator of lipid metabolism. They also raise the question of how accumulation of 4-HC reported in Niemann Pick type C patients may over-activate mTORC1 in this disease.. Possible dysregulation of mTORC1 through 4-HC overproduction could enhance NPC1 pathogenesis, as well as contribute to other metabolic diseases e.g. obesity and diabetes. Further investigation of 4-HC biology is necessary to fully elucidate the significance of 4-HC in normal and disease settings.