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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 known as mTORC1. mTORC1 constantly monitors the available cellular building materials, such as amino acids, lipids and sugars, and changes the speed 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 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 prompt us to follow up on the effects of a cholesterol storage disorder known as Niemann-Pick type C on 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 a unique position to shed new light on the mechanisms of Niemann-Pick disease pathogenesis.

As mTORC1 promotes lipid synthesis and NPC1 promotes cholesterol trafficking, this new link between mTORC1-NPC1 implies a significant impact of their activity on cholesterol metabolism. Cholesterol metabolism is known to be regulated by cholesterol derivatives called oxysterols. An intuitive question that arise is from our discovery is whether oxysterols can synergize with cholesterol in regulating lipid biosynthesis via mTORC1 and NPC1. To address these questions we screened a group of oxysterols and tested their influence on the activity of mTORC1 and NPC1. This screen led us to the identification of a cholesterol-derived molecule known as 4-Hydroxycholesterol (4-HC), which can activate mTORC1 specifically and, moreover, it can inhibit NPC1. Additionally, 4-HC can re-route the cell's metabolism to accumulate more lipids

These functions of 4-HC are completely novel as they had not been observed before. Because the levels of this metabolite in mammalian blood are high, our findings suggest that 4-HC can be an important regulator of lipid metabolism in physiological contexts. It also raises the possibility that elevated

levels of 4-HC may contribute to the pathogenesis of Niemann-Pick disease by simultaneously activating mTORC1 and inhibiting NPC1.

We believe that our investigations of mTORC1 biology will allow us to evolve our understanding of Niemann-Pick disease from a lysosomal storage disorder to a broader disorder of cellular metabolism, and that they may contribute to the design of novel therapeutic approaches toward this disease.