Big or Small, mTOR Signals Them All to Grow

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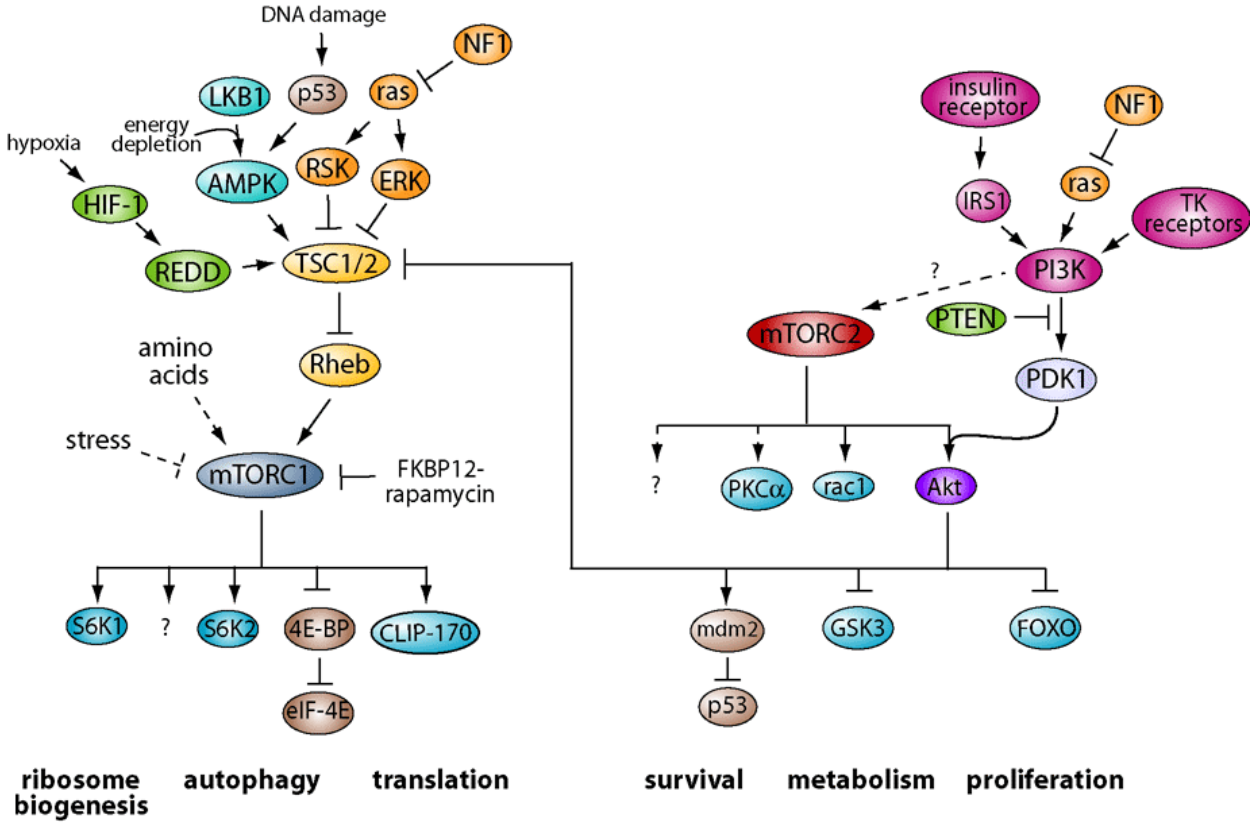
At Pittsburgh University's Science Conference, I had the pleasure to hear from Dr. David M. Sabatini from Massachusetts Institute of Technology (MIT). He started off his speech by talking about a discovery made in his undergraduate career about a bacterium that possessed anti-aging properties. This compound, rapamycin, was isolated from a *Streptomyces* bacterium and found to prevent restenosis of coronary vesicles by stopping the blood vesicles from growing. Lots of people took fascination to this growth stunt and viewed it as the "Forever Pill" which could keep themselves from aging.

Dr. Sabatini wanted to take a better look at exactly how rapamycin could accomplish this task. What he and his lab found was that mTOR seemed to be at the center of any breaking down or building up done in a cell which, in-turn, effects the growth rate. From then on, one of his main focuses at his lab in MIT was to find out how the mTOR pathway is regulated and what kind of outcome it has on growth. Below is a diagram showing the current findings about the mTORC1 and mTORC2 pathways which I will be further discussing.



The mTOR-containing complexes mTORC1 and mTORC2 are at the center of many disease-related signaling pathways, and play fundamental roles in controlling cell growth and proliferation.

https://biology.mit.edu/people/david_sabatini#overview

A study was done in Dr. Sabatini's lab that perturbed the mTOR pathway in mice to see its effect on liver size. They found the inhibiting or assisting the mTOR pathway lead to an increase (assisting) or decrease (inhibiting) in liver size. The decrease in liver size due to inhibition had the same outcome as a liver where the animal had been fasting. This lead Sabatini to believe that the mTOR pathway could be one of the main systems connected to the nutritional state.

The next great finding was that mTORC1 is expressed on the surface of lysosomal membranes when there are nutrients. In order for this to happen, a signal from the obligatory heterodimer RAS must be present. This signal recruits both mTOR and GTPase to the membrane surface of the lysosome to activate growth factor.

Which nutrients are essential to the mTOR pathway was also studied in a mouse model where transgenic $RagA^{GTP/GTP}$ mice without the mTOR pathway gene, heterogeneous for the mTOR pathway gene, or possessing the mTOR pathway were observed. When starved, mice without the mTOR pathway gene or heterogeneous for the mTOR pathway gene were not able to survive as long as mice who possessed the mTOR pathway gene. By giving the mice amino acids, mice who possessed the pathway could be rescued, but it was not known which amino acids specifically helped to rescue the pathway. When further looked at, it was found that no single amino acid could activate the mTORC1 pathway; not even any combination of two amino acids could activate it. Finally, it was found that the combination of Leucine, Arginine, and Lysine were able to activate the pathway.

One of the big implications of finding out how the mTOR pathway works, is the fact that it could have medicinal implications. Pancreatic cancer is a fast developing and extremely deadly disease. This type of cancer usually likes to get their amino acids by lysing their lysosomes. Proper functioning mTORC1 prevents pancreatic tumors from forming. This pathway could be a potential target for pancreatic cancer treatment. Some future work for Dr. Sabatini and his lab would be to try to answer the following questions: why does arginine have two sensors in the pathway and can we make small molecules that mimic the absence of amino acids?