Seminar Date: 10.20.2017
Speaker: David M. Sabatini, MD, PhD.
Title: "Regulation of Growth by the mTOR Pathway"
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Significant Roles of mTORs

David M. Sabatini, MD, PhD, is a well-known scientist for his contributions in the study of the mechanistic target of rapamycin, or the mTOR pathway, which is a key regulator of cell growth and proliferation. He is currently a professor of Biology at M.I.T. and has been awarded many times including the 2017 Dickson Prize in Medicine by the University of Pittsburgh in the beginning of his presentation at Pitt Science.

The main functions of the mTOR signaling pathway are related to almost everything in the cell like growth control, metabolism and aging. Its deregulation is also associated with important diseases such as cancer and diabetes, therefore this research has been drawing great attention from the scientific environment, media and commercial world as well. The mTOR has a long history, since rapamycin produced by *Streptomyces hygroscopicus* was found for the first time in the soil of Easter Island in the 1970s by Surendra Sehgal. Rapamycin is a highly important drug in medicine, especially in organ transplantation, due to its immunosuppressive, antifungal and anti-cancer properties. It has been reported that rapamycin extends life-span in model organisms, prevents narrowing of coronary vessels and stops cell division through inhibition of the mTOR cellular pathway. The Sabatini Lab discovered the roles of particular proteins and also important components of mTORC1 and mTORC2 complexes in this pathway (Figure 1).

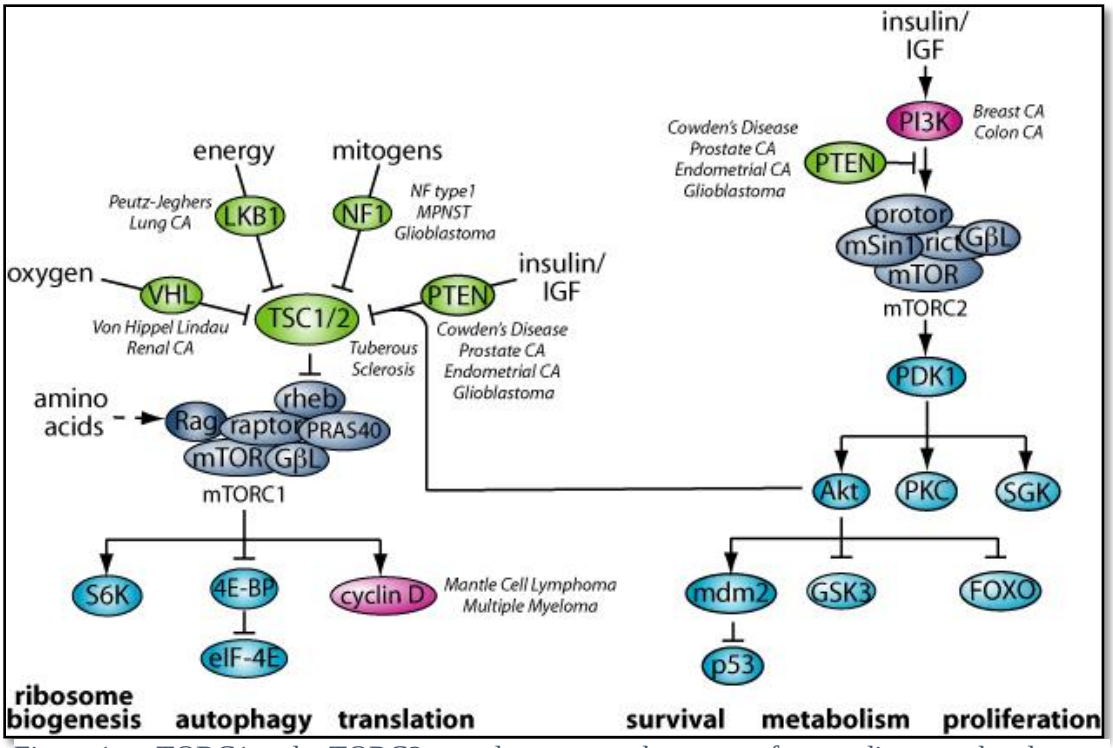

Figure 1. mTORC1 and mTORC2 complexes are at the center of many disease-related signaling pathways, and play significant roles in controlling cell growth and proliferation

First, rapamycin binds to FKBP12 protein and creates a complex that later interacts with mTORC1 which is a large protein kinase. The mTORC1 phosphorylates the 4EBP1 and S6K1 which are two mammalian proteins and the effectors of mTORC1. When researching how signal interaction happens between growth factors and mTORC1, the Sabatini Lab found that majority of them occur through the tumor suppressors called TSC which is an inhibitor of a small GDP, rheb. The rheb is also a direct activator of mTOR. It has been demonstrated that amino acids are also required to initiate the mTOR signaling by interacting with RagGTPase. In other words, rag proteins are necessary to mediate amino acid signaling to mTORC1. Then, Dr. Sabatini showed a movie to explain how they have measured all these findings. They observed that if there are amino acids in the cell, mTORC1 speckles form rapidly on the surface of the lysosome without going to inside the cell, but they leave the surface, if there is no amino acid.

According to their first predicted model, amino acids, growth factors, RagGTPases, oxygen and energy decide whether mTORC1 will be activated or not. However, they have observed that mTORC1 could be activated without an amino acid and RagATPases by adding a target sequence. After this discovery, his research team's studies have focused on the amino acid sensors. They did in-vitro assays and found that amino acids are transported into the lysosomal lumen. Also, loss of amino acid sensing was observed in some cancer cell lines. When they mutated mice by creating knock-in $RagA^{GTP/GTP}$ mice, their survival (%) over time was almost half of those of wild type. This finding showed that hyperactivation of mTORC1 is also a problem, but can be cured by giving rapamycin the mice. Ultimately, all in vivo experiments have presented that neonatal nutrient homeostasis and survival depend on the RagGTPases.

When they have extended their study on the role of amino acids, it has been demonstrated that neither a single amino acid nor combinations of two amino acids are sufficient to completely activate mTORC1. Only combination of leucine, arginine and lysine amino acids can activate mTORC1 signaling. Next, the Sabatini Lab has discovered the sensor molecules that convey amino acids sufficiency to mTORC1. Firstly, sestrin and CASTOR have been found as the direct amino acid sensors for leucine and arginine, respectively. After that, SLC38A9, which is a lysosomal membrane protein with homology to amino acid transporters, has been found as another lysosomal arginine sensor.

Amino acids sensors in the mTORC1 pathway are very complicated systems, because multiple protein complexes regulate the RagGTPases. Some of these protein complexes discovered by his research team consist of GATOR, KICSTOR and CASTOR proteins. The molecules associated with the mTOR pathway may cause many different diseases such as hypopigmentation, facial fibromas, kidney cancer, ovarian cancer, glioblastoma, familial epilepsy and brain malformations as well as cancer and diabetes. As a summary, mTORC1 and mTORC2 complexes have significant roles in controlling cell growth and proliferation, so regulate many disease-related signaling pathways.

He absolutely deserves huge recognition due to his distinguished and continuing achievements in this field, especially when we consider the possible cures for aforementioned

diseases. Dr. Sabatini finished his presentation by pointing out their future implementations which include a search of why arginine has two sensors. His team is also planning to study on small molecules that could mimic the absence of amino acids. In addition to these exciting ideas, Dr. Sabatini and his colleagues are curious about what and how other organisms sense amino acids. For anyone interested in his research can find Dr. Sabatini's all recent and previous publications in this website; http://sabatinilab.wi.mit.edu/publicationsDS.html. Finally, I would like to add that it was such an amazing coincidence, since we have just had a mid-term exam in our core course and there was a question related to the mTOR signaling system. A few days later, we had a chance to attend a seminar presented by Dr. David Sabatini who is the discoverer of the mTOR pathway.

References

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