PROFILE

Profile of David M. Sabatini

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As a young doctoral candidate at the Johns Hopkins University School of Medicine, David M. Sabatini was allowed to choose his own research project for his thesis. He chose to investigate the molecular mechanism of rapamycin, a compound with antifungal, antitumor, and immunosuppressant properties. The decision was pivotal, because Sabatini went on to discover the mechanistic target of rapamycin (mTOR) protein and signaling pathway, which serves as a central regulator of cell metabolism, growth, and proliferation.

Sabatini, a professor of biology at the Massachusetts Institute of Technology (MIT) and a member of the Whitehead Institute, and his team subsequently identified two distinct multiprotein complexes that contain mTOR, as well as associated proteins involved in nutrient sensing. Because the mTOR pathway is activated during numerous cellular processes and deregulated in aging and diseases, such as cancer, epilepsy, and diabetes, his research has attracted broad interest. In recognition of his research achievements, Sabatini received the National Academy of Sciences (NAS) Award in Molecular Biology in 2014, and was elected to the NAS in 2016. His Inaugural Article (1) describes the development of the mTOR and nutrient sensing fields from their inception to the present.

David M. Sabatini. Image courtesy of Ceal Capistrano (Whitehead Institute for Biomedical Research, Cambridge, MA).

Family of Scientists

Sabatini's parents, David D. Sabatini and Zulema Sabatini, are scientists who immigrated to New York from Buenos Aires. His father is a professor emeritus of cell biology at New York University, and his mother is a pathologist. His brother, Bernardo Sabatini, is a professor of neurobiology at Harvard Medical School. Sabatini says, "[My father], of course, influenced me by discussing his work at home and taking us on frequent trips all over the world, where he would attend a scientific meeting and my brother and I would sightsee with my grandmother." Sabatini also recalls helping his mother with the administrative part of her business and learning medicine from her. "So, between my parents," he says, "we saw the world of basic science and medicine, and perhaps not surprisingly, both my brother and I decided to become MD/PhDs."

Sabatini attended Brown University for his undergraduate studies, and spent time in the laboratory of cell biologist Albert Dahlberg. Dahlberg, now a professor emeritus of medical science, was then focusing on ribosomal RNA research. "I loved the feeling of the lab as a home base around which a lot of my work and social life revolved," Sabatini says.

Discovery of mTOR

After receiving a bachelor's degree in biology from Brown in 1990, Sabatini went to the Johns Hopkins University School of Medicine for his graduate studies. Solomon Snyder, a professor of neuroscience, was his thesis advisor. "He always had a very big picture view of science and saw the value in trying things," Sabatini says. "I like this way of doing science and have tried to emulate it. He was interested in everything, and had few biases for what had to be true or not."

Snyder allowed Sabatini to choose a research direction. Sabatini, thinking he was going to be a practicing physician, was at first interested in the medical applications of rapamycin. The compound is produced

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by the bacterium *Streptomyces hygroscopicus*, which was isolated from an Easter Island soil sample. Using rapamycin and its binding partner protein FKBP12, Sabatini purified the protein RAFT1 from rat brains, and found that it is homologous to the proteins encoded by the yeast TOR genes identified in genetic screens for rapamycin resistance (2). Other researchers also identified the same protein, whose name was changed from RAFT1 to mTOR in consultation with the HUGO Gene Nomenclature Committee.

Discovery of mTOR Complexes

Upon receiving his medical and doctorate degrees in 1997, Sabatini started his own laboratory as a Whitehead fellow at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts. In 2002, he became a member of the Whitehead Institute and also joined the faculty of MIT. The same year, he discovered mTORC1, a multiprotein complex nucleated by mTOR (3). Sabatini and his colleagues demonstrated that mTORC1 is a master regulator of cell growth and metabolism. The complex positively controls protein synthesis through various downstream effectors; helps to regulate lipid synthesis, mitochondrial metabolism, and biogenesis; and has other key functions. Other research teams have demonstrated that mTORC1 inhibition increases autophagy and improves the longevity of multiple species.

Sabatini and his team subsequently reported the discovery of another multiprotein complex nucleated by mTOR: mTORC2 (4). Comprised of six different proteins, this complex regulates various biological processes, including cell survival, metabolism, and proliferation. His laboratory also found that mTORC2 is necessary for the development of tumors with activation of the PI3K signaling pathway. Rapamycin and other mTOR inhibitors are now used to treat many diseases, including certain cancers, coronary restenosis (artery blockages), and rheumatoid arthritis. Because mTOR inhibitors are immunosuppressants, they are also administered following organ transplantation to prevent rejection.

Seminal Research on Nutrient Sensing

By 2008, Sabatini was an associate professor with tenure at MIT and an investigator at the Howard Hughes Medical Institute, in addition to his position at the Whitehead Institute. He continued to study mTOR, focusing on mTORC1. Sabatini notes that the most fascinating aspect of this complex has always been that it is regulated by nutrients. He was eager to understand the molecular mechanisms underlying its nutrient sensing. Sabatini and his team found that the signaling enzymes, known as Rag GTPases, are key mediators of nutrient sensing by mTORC1 (5). Sabatini says, "This discovery broke open the black box around nutrient sensing and represents the beginning of our molecular understanding of it."

Four years later, Sabatini earned a full professorship at MIT. Shortly thereafter, in 2015, he and his colleagues discovered the first known nutrient sensor upstream of mTORC1: the lysosomal membrane protein SLC38A9 (6). The finding suggests a model in which mTORC1, located at the surface of lysosomes, receives "go/no-go" signals from the Rag GTPases. SLC38A9 senses arginine, and the protein functions upstream of the Rag GTPases. Sabatini's group then discovered that the protein Sestrin2 senses leucine, an amino acid that modulates muscle growth, appetite, and insulin secretion (7). The identification of SLC38A9, Sestrin2, and another sensor called CASTOR1 (8) were high points in his career, he says. "We had chased these sensor proteins for almost 10 years." For his work on mTOR and nutrient sensing, Sabatini received The Dickson Prize in Medicine and The Lurie Prize for Biomedical Sciences in 2017.

Development of New Technologies

Over the years, Sabatini's research has included the development and application of new technologies to facilitate the analysis of gene function in mammalian cells. For example, his group was a founding member of a consortium of laboratories that developed genome-scale RNA interference libraries targeting human and mouse genes. Collaborating with scientists from the Broad Institute, Sabatini and his team employed the CRISPR genome-editing system to enable genome-scale loss-of-function screening in mammalian cells and identified genes essential for the survival and proliferation of cancer cells (9). He has also applied genetics to numerous questions in metabolism, including the function of mitochondria in cell proliferation (10) and the role of serine synthesis in cancer (11, 12).

Recently, Sabatini's team developed a strategy for rapidly isolating mitochondria or lysosomes and detecting the metabolites within them. The method helped determine that pancreatic cancer cells require SLC38A9 to form tumors because, in addition to being an arginine sensor, SLC38A9 is also needed to eject essential amino acids from lysosomes (13). The research implicates SLC38A9 as a potential pancreatic cancer drug target. Following research on how high-fat diets can promote the initiation of intestinal tumors (14), Sabatini's group is also investigating mechanisms that link obesity to cancer.

Ongoing mTOR Research

While Sabatini's work interests are expanding, much of his efforts are still focused on the mTOR pathway. Despite the numerous advances made by his team and others, many important questions remain unanswered. "We would like to define all of the nutrients sensed by mTORC1 and their sensors," he says. "We would like to understand why lysosomes play such an important role in sensing. What is the benefit to the cell? How did this evolve?" He adds that he and his team would also like to better understand how sensing operates in vivo, such as identifying which tissues sense which nutrients, and why.

Sabatini and his team are poised for the challenges that lie ahead. He expresses gratitude for his colleagues' encouragement and support: "I have been blessed with an amazing group of lab members that make my job easy."

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