Profile of Raymond J. Deshaies

Christopher Samoray, *Science Writer*

Protein homeostasis is crucial to the health of living cells, and dysregulated protein homeostasis can trigger diseases, including cancer. Biochemical cell biologist Raymond Deshaies has devoted his distinguished career to the analysis of protein homeostasis and the development of therapeutic approaches to counter diseases that result when homeostasis goes awry. Deshaies has served as a professor at the California Institute of Technology (Caltech) and as an investigator at the Howard Hughes Medical Institute. Over the years, in addition to devoting his attention to cancer research, he has launched two companies focused on developing cancer-fighting drugs. Recently, he accepted a leadership position at the pharmaceutical company Amgen, Inc. In 2016, Deshaies was elected to the National Academy of Sciences. However, despite his scientific accomplishments and accolades, Deshaies says science is something he "grew into."

Sowing Scientific Seeds

One of four boys, Deshaies grew up in Waterbury, CT. His parents, both French-Canadian, owned a three-story house in the city. His father worked at local factories, and his mother, who only spoke French to him, sold beauty products and took care of the household.

Deshaies' father, who had grown up on a farm, kept a small garden in the yard. "He would spend an inordinate amount of time on this tiny little piece of land," Deshaies recalls. By the time Deshaies reached high school, he, too, had cultivated a green thumb. He not only had taken over the gardening in the yard but also had started growing house plants and accompanying a neighbor on her searches for dahlias.

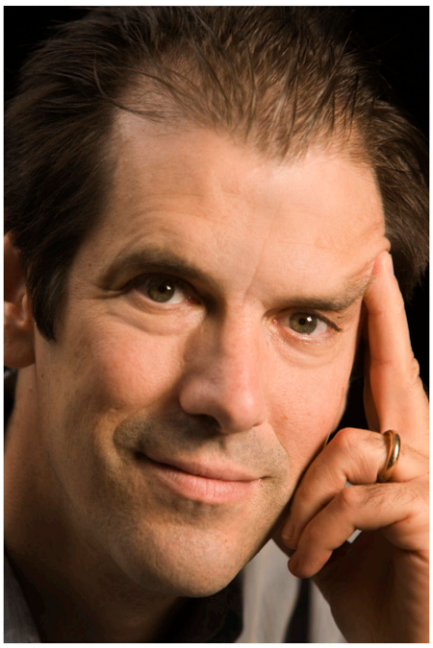
As high school graduation approached, the family expected that, like his brothers, Deshaies would attend the University of Connecticut. However, following the advice of an acquaintance, Deshaies applied to the agricultural school at Cornell University and was accepted on scholarship.

At Cornell, he gravitated toward biochemistry. Unsure of his career goals, during the summer following his junior year, he took on a research assistant position in the laboratory of plant biochemist André Jagendorf, a move that piqued his interest in research and motivated him to apply to graduate school.

Focus on Protein Translocation

Deshaies enrolled in the biochemistry doctorate program at the University of California, Berkeley and set his mind on joining the laboratory of Randy Schekman, a cell biologist who went on to receive the 2013 Nobel Prize in Physiology and Medicine. In Schekman's laboratory, the primary focus was on protein secretion in yeast. "I was hell-bent to get into his lab," Deshaies says.

Deshaies was offered a position in the laboratory. During this time, he came up with the idea of performing a screen to identify yeast genes required for the translocation of secretory proteins into the endoplasmic reticulum (ER), a cellular organelle involved in protein assembly. Deshaies reasoned that a search for translocation mutants might lead to the discovery of a putative channel for the transport of proteins across the ER membrane. Deshaies jotted the idea down on a piece of paper and put it under Schekman's door.



Raymond J. Deshaies. Image courtesy of Paul Fetters Photography.

Two months later, Deshaies found a message on his desk from Schekman: "See me when you get in." Schekman had just heard a seminar speaker describe a way to implement Deshaies' idea and asked if Deshaies wanted to take on the project. The project led to the discovery of *sec61* (1), a yeast mutant bearing a mutation in the gene encoding Sec61, a component of the proteinaceous channel that moves secretory proteins across the ER membrane.

Deshaies says graduate school and his time in Schekman's laboratory affirmed that science was the career for him. "He has been the single most influential person in my career development," Deshaies says of Schekman. "I owe an enormous debt of gratitude to Randy. Being in his lab was transformative. It was a fantastic experience, and he was a fantastic mentor."

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 3565 in issue 14 of volume 114.

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Deshaies obtained his PhD in 1988 and for the next two years stayed on as a postdoctoral researcher at Berkeley. He continued to study protein translocation mutants as well as how proteins involved in the environmental stress response affect membrane translocation and assembly (2, 3).

Refining Technique

In 1990, Deshaies took on another postdoctoral position across San Francisco Bay, at the University of California, San Francisco. There, he worked with Marc Kirschner, now the chair of the Department of Systems Biology at Harvard University. Deshaies set out to study the cell cycle. Specifically, he wanted to reconstruct the activation of G1-phase cyclin-dependent kinase, CDK, a protein involved in regulating the cell cycle.

Kirschner's laboratory had recently found success in activating mitotic CDK in frog extracts by adding bacteria-produced mitotic cyclin. The activation occurred only after a substantial delay and above a certain cyclin concentration threshold, hinting that posttranslational regulatory mechanisms were involved in the activation process. Deshaies reasoned that using G1 cyclin to prompt CDK activation in G1-phase yeast extracts might yield new insights into CDK regulation. Although he was successful in prompting G1 CDK activation, there was no lag time or concentration threshold for activating CDK using G1 cyclin, leading him to conclude that the experiments were unlikely to reveal new regulatory mechanisms.

While conducting the experiments, however, he developed a method for making yeast cell extracts that lacked G1 cyclin, a protein normally produced at the beginning of the cell cycle. When he needed to switch on yeast G1 CDK activity, he simply added G1 cyclin back to the extract. By incorporating a radiolabeled G1 cyclin protein into the assay, he observed that it became extensively ubiquitylated upon activating CDK; ubiquitin, a small protein made of 76 amino acids, is highly conserved from yeast to humans and helps trigger the degradation of old or damaged proteins.

Before Deshaies' observation of G1 cyclin ubiquitylation, Kirschner's laboratory observed that mitotic cyclins became ubiquitylated and degraded during mitosis. The cyclin degradation, the researchers found, was essential for exiting mitosis. Moreover, additional research in yeast suggested that the ubiquitin-conjugating enzyme, Cdc34, carried a cell from the G1 phase to the next phase in the cell cycle, the S phase, in which DNA is copied. Around the same time, geneticist Kim Nasmyth, now at the University of Oxford, published a genetic model demonstrating how yeast cells advance from the G1 to the S phase of the cell cycle (4). The model featured elimination of a CDK inhibitor, which freed CDK to promote DNA replication. However, the model lacked direct biochemical evidence for how the process occurred.

Deshaies' assay for G1 cyclin ubiquitylation provided a means to investigate the ubiquitylation-promoting activity of genes required for progression from the G1 to the S phase. Later, after Deshaies joined Caltech, the work contributed to another important finding. "It opened the door to the discovery of the first member of the large family of SCF cullin–RING ubiquitin ligases," Deshaies says.

Deshaies started at Caltech in 1994. He focused on the G1–S phase transition of the cell cycle. In particular, he turned his attention to a handful of proteins, including Cdc4, Cdc53, and later Skp1, which were known to play a role in the G1–S transition of the cell cycle. In 1997, in studies that used methodology from his yeast assay, Deshaies and colleagues reported that Cdc4, Cdc53, and Skp1 together formed a ubiquitin ligase complex, which they named "SCF" (5).

The SCF complex, the researchers found, drove ubiquitylation of phosphorylated Sic1 protein, a key player affecting the G1–S transition phase. The discovery lent further clarity to the biochemical processes regulating entry into S phase. "We put biochemical meat on the genetic bones of the Nasmyth hypothesis and showed exactly what are the key regulatory events that underlie the G1–S transition in yeast," Deshaies says.

Business Endeavors

Deshaies continued work on the cell cycle, but the discovery of SCF drew him further into the ubiquitin world. Around 2003, by which time he was also an investigator at the Howard Hughes Medical Institute, his group had ramped up research on ubiquitin. "I felt there was more opportunity to make fundamental contributions with a little bit more elbow room," Deshaies says.

During this period Deshaies was also busy developing a biotechnology company, Proteolix, Inc. The company was a result of collaboration between Deshaies and Craig Crews, a chemical biologist at Yale University. Each brought to the company an independent piece of intellectual property and PROTACs, a joint piece of intellectual property that now is gaining traction in industry. Proteolix focused on a compound identified by Crews, and from their efforts emerged Kyprolis, a prescription medicine for patients with relapsed multiple myeloma, a recurrent blood cancer that affects plasma cells in the bone marrow.

Kyprolis works by inhibiting the proteasome, which degrades proteins conjugated with ubiquitin. Although the details of the drug's cancer-fighting mechanisms are not fully understood, the general thinking is that, by blocking protein degradation in cancerous cells, Kyprolis triggers catastrophic accumulation of damaged proteins, leading to cell death.

In 2012 the US Food and Drug Administration approved Kyprolis. Recently, Kyprolis was reported to extend the lifespan of relapsed multiple myeloma patients nearly 8 months longer than its predecessor, bortezomib (6).

In 2011 Deshaies helped start another company, Cleave Biosciences. Similar to Proteolix, Cleave focuses on inhibiting cellular factors that mediate protein degradation. The company is exploring how inhibiting p97/VCP, an enzyme involved in protein quality control, might help treat multiple myeloma and other cancers.

In his Inaugural Article, Deshaies and colleagues report that p97 promotes the degradation of ubiquitylated glutamine synthetase (GS), an important player in cellular metabolic processes (7). GS is ubiquitylated by $CRL4^{CRBN}$, the protein target of lenalidomide, another drug used to treat multiple myeloma. Deshaies suspects that targeting p97 could offer a higher degree of specificity than targeting the proteasome in the treatment of multiple myeloma, and Cleave Biosciences is working on developing p97 inhibitors. "It gives us another player to think about in that whole therapeutic axis," Deshaies says.

In May 2017, Deshaies left Caltech to accept a senior position at the pharmaceutical company Amgen, Inc., which markets Kyprolis. There he will oversee early scientific discovery work spanning a variety of diseases, including cancer, inflammation, neurodegeneration, and cardiovascular disease.

Despite his busy schedule, Deshaies enjoys gardening, skiing, fishing, hiking, and backpacking. His favorite pastime is mountain biking in the San Gabriel Mountains. Deshaies says scientific research is a lot like mountain biking: The more effort you put in, the better you get at overcoming seemingly insurmountable challenges.

1 Deshaies RJ, Schekman R (1987) A yeast mutant defective at an early stage in import of secretory protein precursors into the endoplasmic reticulum. *J Cell Biol* 105:633–645.

2 Deshaies RJ, Schekman R (1989) *SEC62* encodes a putative membrane protein required for protein translocation into the yeast endoplasmic reticulum. *J Cell Biol* 109:2653–2664.

3 Deshaies RJ, Koch BD, Werner-Washburne M, Craig EA, Schekman R (1988) A subfamily of stress proteins facilitates translocation of secretory and mitochondrial precursor polypeptides. *Nature* 332:800–805.

4 Schwob E, Böhm T, Mendenhall MD, Nasmyth K (1994) The B-type cyclin kinase inhibitor p40SIC1 controls the G1 to S transition in S. cerevisiae. *Cell* 79:233–244.

5 Feldman RM, Correll CC, Kaplan KB, Deshaies RJ (1997) A complex of Cdc4p, Skp1p, and Cdc53p/cullin catalyzes ubiquitination of the phosphorylated CDK inhibitor Sic1p. *Cell* 91:221–230.

6 Amgen (2017) Amgen presents overall survival data from KYPROLIS (carfilzomib) phase 3 ENDEAVOR trial at 16th international myeloma workshop. Available at https://www.amgen.com/media/news-releases/2017/03/amgen-presents-overall-survival-data-from-kyprolis-carfilzomib-phase-3-endeavor-trial-at-16th-international-myeloma-workshop/. Accessed May 9, 2017.

7 Nguyen TV, et al. (2017) p97/VCP promotes degradation of CRBN substrate glutamine synthetase and neosubstrates. *Proc Natl Acad Sci USA* 114:3565–3571.