Biography of Stephen J. Elledge

Over the past century, researchers have invested substantial efforts toward understanding the cell cycle. However, only recently have these studies gained a molecular foothold. Leading the research in this field is Stephen J. Elledge, professor of genetics at Harvard Medical School and Brigham and Women's Hospital in Boston. Playing the dual roles of inventor and investigator, Elledge developed original techniques to define what drives the cell cycle and how cells respond to DNA damage. By using these tools, he and his colleagues have identified multiple genes involved in cell-cycle regulation.

Elledge's work has earned him many awards, including a 2001 Paul Marks Prize for Cancer Research and a 2003 election to the National Academy of Sciences. In his Inaugural Article (1), published in this issue of PNAS, Elledge and his colleagues describe the function of Fbw7, a protein involved in controlling cell proliferation. These findings add to the growing cache of cell-cycle knowledge with implications for cancer research.

Biology vs. Chemistry

Growing up in Paris, IL, in the 1960s, Elledge's chemistry set ranked high among his favorite toys. He was fascinated by the atomic nature of matter and took great pleasure in the fact that molecules could be split and recombined into almost unlimited permutations. Elledge tried to absorb as much information about chemistry as his early understanding would allow. "I went to the public library and checked out a chemistry book when I was in elementary school," he said. "I tried to learn it, but I couldn't. It was just too complicated."

Elledge's cognitive abilities caught up with his natural curiosity in high school, and he eventually chose chemistry as his major at the University of Illinois in Urbana–Champaign. One of Elledge's college roommates, whose major was pre-med, frequently expounded on the virtues of life sciences. Elledge was not interested at first. "I always ignored him because I thought biology was soft science," he said. However, during his junior year abroad at the University of Southampton in England, Elledge gave biology a try by taking an introductory course and a semester of genetics. The classes sparked an interest, which he kept alive by taking a biochemistry class on his return to the United States. It

Stephen J. Elledge

was during his biochemistry lectures that Elledge first heard about recombinant DNA. "I just thought it was fabulous," he said. "Once biology got down to being molecular, then it intersected with my interests."

After receiving his bachelor's degree in 1978, Elledge applied to graduate programs in biology and chemistry. Although he had not yet decided on which field to focus, he chose to continue his studies at the Massachusetts Institute of Technology (MIT) Biology Department. "I didn't know what I wanted to do, but they had a lot of people, so I figured I'd be able to sort it out," he said. Elledge ended up working with bacterial geneticist Graham Walker. For his thesis, Elledge studied the error-prone DNA repair mechanism in *Escherichia coli* called SOS mutagenesis. His work identified and described the regulation of a group of enzymes now know as error-prone polymerases, the first members of which were the *umuCD* genes in *E. coli* (2–4).

Elledge's schedule at MIT allowed him time for side projects, and he used the opportunity to develop a new cloning tool. His creation was spurred by the frustration of unsuccessfully trying to use two existing tools, lambda phage and bacterial plasmid libraries, to clone the *umuC* gene, which produces proteins necessary for UV and chemical mutagenesis in *E. coli*. By combining the tools, Elledge invented a technique that allowed him to approach future cloning problems of this type with great rapidity (5). With the new technique, "you could make large libraries in lambda that behave like plasmids. We called them 'phasmid' vectors, like plasmid and phage together," said Elledge. The phasmid cloning method was an early cornerstone for molecular biology research.

From Disappointment to Delight

In 1984, Elledge began a postdoctoral fellowship at Stanford University (Stanford, CA) with mentor Ronald Davis. "Davis is an inventor," said Elledge. "We had a lot in common because I'm interested in developing new technologies and so is he."

Elledge soon began working on homologous recombination, an important niche in the field of eukaryotic genetics. Working with the yeast genome, Elledge searched for *rec A*, a gene that allows DNA to recombine homologously. Although he never located *rec A*, his work accidentally led him to a family of genes known as ribonucleotide reductases (*RNRs*), which are involved in DNA production (6). *Rec A* and *RNRs* share the same last 4 amino acids, which caused an antibody crossreaction in one of Elledge's experiments. Initially disappointed with the false positives in his hunt for *rec A,* Elledge was later delighted with his luck. He found that *RNRs* are turned on by DNA damage (6), and that these genes are regulated by the cell cycle (7). "It was just serendipity," he said.

Elledge's work in this area led to a job offer from Baylor College of Medicine, Houston, in 1989. Prior to leaving Stanford, Elledge attended a talk at the University of California, San Francisco, by Paul Nurse, a leader in cell-cycle research who would later win the 2001 Nobel Prize in medicine. Nurse described his success in isolating the homolog of a key human cell-cycle kinase gene, *Cdc2*, by using a mutant strain of yeast (8). Although Nurse's methods were primitive, Elledge was struck by the message he carried: that cell-cycle regulation was functionally conserved, and that many human genes could be isolated by looking for complimentary genes in yeast. Elledge then took advantage of his past successes in building phasmid vectors to build a versatile human cDNA library that could be expressed in yeast.

In his first experiments after setting up a laboratory at Baylor, he introduced this library into yeast, screening for

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This is a Biography of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 3338.

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complimentary cell-cycle genes. He quickly identified the same *Cdc2* gene isolated by Nurse. However, Elledge also discovered a related gene known as *Cdk2*. Elledge subsequently found that *Cdk2* controlled the G_1 to S cell-cycle transition, a step that often goes awry in cancer. These results were published in the *EMBO Journal* in 1991 (9). "It was one of the biggest papers I've had," said Elledge.

Elledge also continued to capitalize on his unexpected discovery of *RNRs* and used them to perform genetic screens to identify genes involved in sensing and responding to DNA damage. He subsequently worked out the signal transduction pathways in both yeast and humans that recognize damaged DNA and replication problems (10–12). These "checkpoint" pathways are central to the prevention of genomic instability and a key to understanding tumorigenesis.

A Central Motif

Elledge's research caught the attention of Wade Harper, a new member of Baylor's biochemistry faculty. Combining their efforts, Harper and Elledge studied the regulation of *Cdk2*. "I was a geneticist and Wade was a biochemist. Together we were able to accomplish much more than either alone," said Elledge. Elledge revamped a method for detecting protein interactions, known as the "two-hybrid system," into a cloning method by combining it with his lambda cloning techniques. By using the new method, Harper and Elledge succeeded in isolating a gene known as *p21*, which they later identified as part of a family of *Cdk2* inhibitors. The gene also was cloned by Bert Vogelstein's laboratory at Johns Hopkins University (Baltimore, MD), who discovered p21 was regulated by the cancer gene *p53*. Elledge and Vogelstein realized the similarity of their findings after chatting on the phone and published articles back-to-back in *Cell* in 1993 (13, 14).

Elledge and his laboratory continued to look for other human genes that complimented yeast cell-cycle regulators. In 1996, his team identified a conserved motif, the F-box, that is present in some proteins. This motif recognizes specific protein sequences and tags them with ubiquitin for destruction. The buildup of certain proteins can sabotage the cell cycle and bring it to a halt; thus, destroying these proteins keeps cells dividing. Further investigation showed that the F-box sequence is ubiquitous throughout evolution. "There were so many F-box proteins that we figured it was going to be very central," he said. Since Elledge's laboratory published its first article on the F-box in 1998 (15), almost a thousand articles have reported investigations of F-box proteins and related ubiquitin ligases. The F-box has been implicated in numerous pathways, including gene expression, the immune response, cell morphology, cancer, and circadian rhythms.

Elledge's focus still centers on the F-box motif and the roles played by its multitude of variations. In his Inaugural Article, found on page 3338, Elledge and his colleagues (1) describe mouse knockouts missing the gene to create an F-box protein known as Fbw7. Previous research suggested that Fbw7 controls the degradation of cyclin E, a protein that drives cell proliferation. By studying the knockouts, Elledge's team showed that Fbw7 controls not only the abundance of cyclin E but also Notch protein. Both of these proteins play key roles in regulating mammalian development.

Elledge's findings add to the growing body of knowledge on how F-box proteins operate in cells. However, with the function of hundreds of different F-box proteins currently unknown, Elledge and his collaborators, including Wade Harper, will have their work cut out for decades more. He and his laboratory plan to continue studying the genetics and genomics of different F-box proteins, elucidating their roles in cell proliferation. Elledge expects that this vast mystery, combined with his regular discoveries, will keep his passion alive. "I'm a scientist. I want to discover new things, and I want to develop new ways of looking at things. That's what makes me excited, and that's what I'm interested in," he said.

Christen Brownlee, *Science Writer*

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