Profile of Xiaodong Wang

"I feel like I'm a postdoc," says biochemist Xiaodong Wang, the George L. MacGregor Distinguished Chair Professor in Biomedical Science at the University of Texas Southwestern Medical Center at Dallas (UT-Southwestern; Dallas, TX). Although the youthful Wang may perhaps be mistaken at first glance for a postdoctoral fellow or newly appointed professor, a closer look back at his impressive career may make one wonder why he would make such a claim. Since he first arrived in Dallas as a graduate student 20 years ago, Wang has produced an extensive series of findings, unraveling many of the mysteries surrounding apoptosis, and his work has revealed a key role for the mitochondria. He has extensively studied the interactions triggering the release of cytochrome *c* from inside this organelle and causing the apoptotic cascade, as evidenced in his Inaugural Article published in a recent issue of PNAS (1).

Elected to the National Academy of Sciences in 2004, Wang's humility in the face of his success stems from the people who surround him at UT-Southwestern. "The research environment here is unparalleled," he says, recalling that by the time he had finished his Ph.D. and postdoctoral training, he had already experienced three Nobel Prize celebrations, including one in 1985 for his postdoctoral advisers, Joseph L. Goldstein and Michael S. Brown. "[Researchers here] have done so much for so long, it's just unbelievable how they can keep going," says Wang. He believes that the high standards set by other faculty members provide a great benefit for someone starting a research career. "Not only did they provide the environment and role models for me, they also provided the evolutionary pressure," he says. "Nothing is ever good enough, and you're only as good as your last paper, which I think is great. As long as we keep this kind of mentality, I think we'll be all right."

Beginnings in China

Even before he came to Dallas, Wang had to deal with lofty expectations. He was born in 1963 in Wuhan in central China to a family that already had three generations of college graduates, both male and female. "That is pretty rare considering the oldest college in China is only 110 years old," says Wang. His various family members earned degrees in numerous disciplines, from a grandfather who studied English to an uncle who was a physicist. But, even before he could think about college, he had to deal with the possibility of not even receiving a secondary education.

Xiaodong Wang

In 1966, just 3 years after Wang was born, Chairman Mao Zedong of China launched his Cultural Revolution, which among other agendas cracked down on so-called "bourgeois intellectuals." The Chinese educational system suffered greatly during this period, as schools were either shut down or altered to teach more "practical" curricula, while teachers and academics, like Wang's family, were dismissed, harassed, or worse. "This was an extremely difficult time," says Wang, "but, in retrospect, I also benefited in a strange way." His great uncle, a biology professor, was removed from his position and sent back to the countryside, where he was forced to make a living as a peasant. "My grandmother sent me to his place on every school break, and we talked on all the subjects I was interested in as a kid," says Wang. "I was influenced by him a great deal," he says of his great uncle, "and [that] probably was a determining factor in why I went to biology."

Only after Wang began high school did things return to normal, with schools again focusing on academics. During that time, Wang developed a penchant for mathematics. "I basically studied math as a hobby. I participated in math competitions and did things like that," he says. He enjoyed the puzzle-solving aspects of mathematics, of being able to methodically work out a solution to any problem. "I like challenges, and I had a really good math instructor . . . who would always challenge me with difficult math questions, and I really enjoyed that process. I think he was the first person who helped me recognize that I have some skill for scientific research," Wang says.

At Beijing Normal University, Wang met another teacher who sparked an interest in biology to match Wang's problem-solving skills. Shaobai Xue was Wang's cell biology teacher and later served as his undergraduate thesis adviser. "In China, every science major in college had to do some research before they could be granted a degree," says Wang, "so I spent my last half year doing my thesis with him." Wang and Xue quickly formed a strong relationship. "His entire family only had one desk at home, so every evening, when his son had to use it to study, he would come over to his office in lab to study himself. I was also often doing research at night, so the two of us got the chance to chat a lot," he says. Through their many conversations, Wang became amazed by Xue's knowledge and scientific foresight. Says Wang, "He made me realize the power of biochemistry. Even though he wasn't able to do a lot of the experiments he wanted in China at that time, he had the right way of thinking. He had me studying histone acetylation for my thesis, which in the early 1980s was really ahead of its time." In 1984, Wang received his bachelor's degree in biology from Beijing Normal University.

Art of Science

With his eyes opened to the power of biochemistry, the newly indoctrinated fourth-generation college graduate decided to pursue a long-term research career, preferably in the United States. "Anybody who was interested in doing research at that time knew that coming over to the United States for graduate school is the right way to do it," says Wang. Although China had reopened its doors to the outside world after the Cultural Revolution, Wang had no formal channels of application at the time.

Wang found an opportunity in the China–United States Biochemistry and Molecular Biology Examination and Administration (CUSBEA) program, which provided 60 scholarships each year to aspiring biologists throughout China. CUSBEA was initiated in 1982 by Ray

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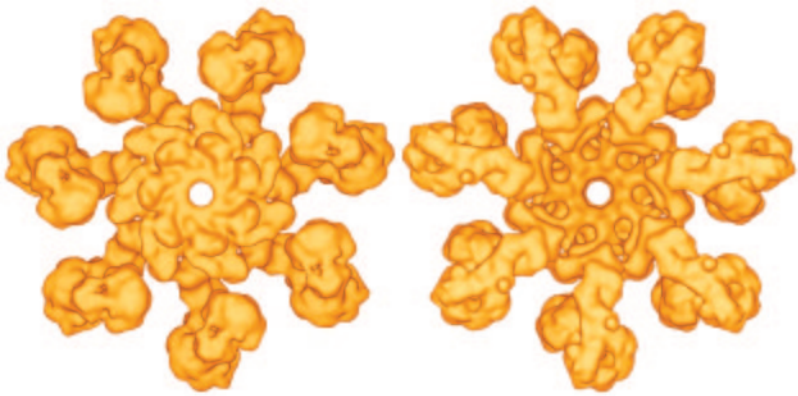
This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 17545 in issue 49 of volume 102.

Wu, an eminent professor at Cornell University (Ithaca, NY) and Chinese émigré who wanted to provide other Chinese scientists with the same opportunity for U.S. research training that he had. After a rigorous screening process, which included two separate entrance examinations and an interview conducted entirely in English by a committee of U.S. college professors, Wang received good news: he was among the top 60 scholars selected, and he came to the United States in 1985.

The CUSBEA program recommended a few possible destinations for Wang based on his expressed interests. Of the possibilities, Wang was most interested in UT-Southwestern, specifically for the chance to work with Joe Goldstein and Mike Brown. "My decision came after I read a *Scientific American* magazine, and that particular issue had an article written by Goldstein and Brown, on the LDL receptor pathway," says Wang (2). "I was fascinated by the level of science they could do. It was almost like an art form."

At the time however, Goldstein and Brown were not taking any graduate students, so Wang joined the laboratory of Richard Padgett, who himself had just arrived at UT-Southwestern's biochemistry department after finishing his postdoctoral training in Phillip Sharp's group at the Massachusetts Institute of Technology (MIT; Cambridge, MA). At MIT, Padgett developed the first *in vitro* mRNA splicing system and began to study pre-mRNA splicing. "I was again fortunate since I got to be his first graduate student," says Wang, "and I got excellent training in modern biochemistry and molecular biology techniques." After receiving his Ph.D. in biochemistry in 1991, Wang joined the laboratory of Brown and Goldstein as a postdoctoral fellow.

At the time, Brown and Goldstein were investigating transcriptional regulation of the low-density lipoprotein (LDL) receptor in response to sterol concentrations, and Wang identified and purified the transcription factor involved in this process, sterol regulatory element-binding protein (SREBP) (3). "It turned out that this transcription factor was membrane-bound, and it has to be proteolyzed to be active. So I was drawn into the proteolysis process," he says. Continued work led Wang to identify the protease that activated SREBP (4), and, after purifying it, he realized he had stumbled into another field. The human homolog of the protease he discovered in hamster cells was CPP32 (caspase-3), which itself was notable for its relation to *C. elegans* CED-3, one of the first two proteins demonstrated to play a role in initiating apoptosis (5).



Views of apoptosome structure.

New Role for Mitochondria

After 4 years of postdoctoral training, Wang accepted his first faculty position as an Assistant Professor at Emory University (Atlanta, GA) in 1995. He would spend only about a year in Atlanta, however, before his old advisers, Goldstein and Brown, along with newly appointed department chairman Steve McKnight, recruited him back to the biochemistry department at UT-Southwestern. Interestingly, even though only one of Wang's 20 years in the United States was at Emory, it was there that he made what he considers one of his most important research findings.

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Wang developed a cell-free system to study the apoptotic process, in hopes of finding the elements responsible for activating CPP32 and initiating apoptosis. He found a 15-kDa protein required for this *in vitro* apoptosis, a protein that turned out to be cytochrome *c* (6). "This was important," he says, "because it established a firm role for the mitochondria, which is the energy workhorse of the cell, for apoptosis." A mitochondrial role had already been hinted at with the discovery of BCL-2, a protein localized to the mitochondrial membrane that prevented cells from undergoing apoptosis. Wang then connected these two proteins when he demonstrated that overexpressing BCL-2 prevented cytochrome *c* release from the mitochondria (7).

Upon returning to Dallas, Wang began adding more pieces to the complex pathway puzzle of mitochondrial activation of apoptosis. In a veritable alphabet soup of studies, he identified and characterized various proteins, including Apaf-1, Bid, and Smac (8–10), among others. In his PNAS Inaugural Article (1), Wang and his group elucidate two biochemical steps in the caspase-activated pathway that forms the apoptosis machinery, or apoptosome. First, Apaf-1, a protein that binds with cytochrome *c* to form the apoptosome after the cytochrome's mitochondrial release to cytosol, is shown to use the nucleotide dATP as a cofactor. "This is really neat," says Wang, because "many other nucleotides have been previously described as cofactors for a variety of cellular functions, but this is the first cellular protein that uses deoxy ATP." Second, Wang demonstrates that this dATP undergoes one round of hydrolysis when cytochrome *c* and Apaf-1 bind together. "We knew these two proteins bound to form the apoptosome, but now we know the binding induces hydrolysis," he explains, "and after hydrolysis you need nucleotide exchange, or else you form aggregates, and this inactivates the whole complex."

Research Worries, Research Future

With the publication of his PNAS Inaugural Article, Wang believes he is at a high point in his career right now. "Ten years ago, when we first discovered cytochrome *c* as an apoptosis inducer, most people, including ourselves, were afraid that what we saw was some kind of *in vitro* artifact," he says. "Today, putting all our work together, I think we understand how cytochrome *c* induces caspase activation in much more molecular detail, and we also obtained solid

genetic evidence that cytochrome *c* is a double agent for energy production and apoptosis" (11). Still, Wang has no plans to rest on his laurels, because he always worries about what the future may bring. "I always ask myself whether each discovery I make will mark the peak of my scientific career. I always have this fear that, before we know it, the peak has passed us by," he admits.

At 42, though, Wang still has plenty of research left ahead of him, and plenty of directions he can take in hopes of finding another peak. "Like all good science," he says, "our findings have raised more questions than answers. 'How widely used is this pathway?' 'Are there other pathways that may get masked by this potent pathway?'" A good deal of his work has looked at the downstream events after cytochrome *c* release, but he is now looking upstream as well, to see how mitochondria respond to different apoptotic stimuli. Such research will hopefully lead to answering the "holy grail" of apoptosis, which, he says, is "why and how a particular cell chooses to undergo apoptosis." As he explains, "I think we are still quite far from the molecular answer."

Wang is also applying the knowledge he and others have uncovered about apoptosis to developing therapeutic cancer drugs. He has already achieved success with the development of a small-molecule mimic of Smac, another mitochondrial protein released to cytosol during apoptosis and which promotes caspase activation by removing caspase inhibitors. "When we first looked at the mode of action of Smac, we realized the functional domain was only the last four amino acids of the N terminus," he says. This finding meant it would be feasible to synthesize a small-molecule mimic, and so, together with departmental colleagues Patrick Harran and Jef De Brabander, Wang designed a chemical called Compound 3. Compound 3 displayed the ability to specifically activate the apoptosis machinery in a variety of cancer cells, killing them (12).

Wang has even branched off a bit in his research and is beginning to study RNA interference, a conserved gene silencing pathway that functions in many cellular processes. With postdoctoral fellow Qinghua Liu and others, Wang found that the enzyme responsible for generating small-interfering RNAs had a previously unknown subunit (13). Liu wanted to call the subunit "R2D2," ostensibly because it has two RNA-binding domains and interacts with the Dicer-2 protein. Although he does not consider himself a big Star Wars fan, Wang agreed that the name was appropriate. "The name really fits the role," he says. "R2D2 is only 50 kDa, compared to Dicer-2, which is 185 kDa, so you have this short little protein that accompanies a longer protein and helps it do its job." Wang notes that he has received many emails from Star Wars fans thanking him for finally naming something after their favorite character. However, even he drew the line when Liu discovered another protein that he wished to call "C3PO" (eventually renamed R3D1). Says Wang, "I told him that, after all, we are—or at least I think we are—serious scientists."

Nick Zagorski, *Science Writer*

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