Profile of Junying Yuan

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Cell biologist Junying Yuan vividly remembers the moment when, during her second year of graduate school at Harvard University in 1983, a thin, restless Huntington's disease patient was wheeled into her "Neurobiology of Disease" class. "I was appalled that modern medicine could do little for him," she says. "He and others suffering from neurodegenerative diseases made a lasting impression on me. I became emotionally motivated to try to help these patients."

Over the subsequent three decades, Yuan and her team have made major discoveries concerning the molecular mechanisms regulating cell death involved in normal development and a wide range of disorders. Her achievements include discovery of the regulated necrotic cell death pathway termed "necroptosis" and its key mediator, the kinase receptor-interacting serine/threonine-protein 1 (RIPK1). She and her colleagues also discovered the evolutionarily conserved role of caspase enzymes in regulating mammalian apoptosis. Elected to the National Academy of Sciences in 2017, Yuan reviews her team's research on RIPK1, a kinase that is now a pharmaceutical target, in her Inaugural Article (IA).

Cultural Revolution Challenges

Yuan was born in Shanghai, China, to a family of scholars. Her father and mother were both professors at Fudan University Shanghai Medical College. Yuan's paternal grandfather Kaiji was an organic chemistry professor at the college.

During China's cultural revolution, a sociopolitical movement from 1966 to 1976, universities closed and many textbooks were burned. The period adversely affected Yuan's family, and Yuan thought factory work or farming was her only vocational option. Her high-school teacher Zhaiyang Lu, however, recognized her talent and urged Yuan to press on with her education. Since the only local science textbooks, dated to before the Cultural Revolution, were locked in the school library, Lu procured the books for her. Before returning them, Yuan pored over the math, physics, and chemistry curricula that she previously had not learned. When China reinstituted college entry examinations, she placed at the top of more than 100,000 other test

Photograph of Junying Yuan. Image courtesy of Aaron Washington for Harvard Medical School.

takers in science in Shanghai. Yuan attended Fudan University, where she majored in biochemistry.

Curiosity About Cell Death

The China-United States Biochemistry Examination and Application (CUSBEA), which lasted from 1982 to 1989, enabled top students from China to attend graduate schools in select universities in the United States and Canada. Yuan scored second out of all of the top graduates who took the test in 1982. She was among the first CUSBEA students admitted to graduate studies in the United States. Her choice was Harvard, where she was initially mentored by neurobiologist Edward Kravitz. He taught Yuan's Neurobiology of Disease class, among others. The courses piqued her curiosity about cell death. She says, "Cell death was not even a field, but it was known that up to 50% of neurons die during normal development. I was intrigued by the possibility that disease-related cell death could be related to certain mechanisms in development."

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Yuan learned about developmental cell death in the nematode *Caenorhabditis elegans* during a 1983 lecture given by Massachusetts Institute of Technology (MIT) biologist H. Robert Horvitz. Yuan says, "A lightbulb went off for me. I realized that *C. elegans* was a perfect organism for the study of cell death using genetics." Because no one at Harvard was studying cell death, she asked Kravitz for permission to spend time in Horvitz's laboratory at MIT. Horvitz became her PhD thesis advisor, although she remained a student at Harvard, where she earned her doctorate in neuroscience in 1989.

Discovery of Mechanism of Apoptosis

Shortly before Yuan's work with Horvitz, he and graduate student Hillary Ellis determined that mutations in the genes *ced-3* and *ced-4* prevent nearly all programmed cell death in *C. elegans* development (1). Horvitz asked Yuan to investigate *ced-3* and *ced-4* as part of her doctoral thesis. Using genetic mosaic analysis, she showed that the genes act autonomously within cells to cause programmed cell death (2). The findings revealed the cellular suicide mechanism. Two additional articles coauthored with Horvitz elucidated the cell death machinery (3, 4). A third, co-led by fellow graduate student Shai Shasham, demonstrated that *ced-3* in *C. elegans* is similar to the human protease interleukin1- β converting enzyme (ICE) (5).

The achievements contributed to Horvitz, along with colleagues Sydney Brenner and John Sulston, receiving the 2002 Nobel Prize in Medicine or Physiology. Yuan traveled with the team to Stockholm for the award ceremony, where Horvitz highlighted her contributions during his Nobel Lecture (6).

Evidence for Mammalian Caspases

Choosing to skip a postdoctoral stint, Yuan accepted an instructor of medicine position at Harvard in 1990 and became an assistant geneticist at Massachusetts General Hospital's Cardiovascular Research Center, where she set up an independent laboratory. Her team's first two articles established ICE, later named caspase-1, as a functional homolog of *ced-3* in controlling the apoptosis of mammalian cells (7, 8). The seminal studies launched the molecular era in cell death research. More than 95,000 articles concerning apoptosis and caspases have since been authored by her team and others.

Yuan and her colleagues have also demonstrated the roles and mechanisms of other members of the mammalian caspase family in regulating apoptosis. For example, they found that two isoforms of *Ich-1*, later named caspase-2, can function to mediate or antagonize apoptosis (9). They showed that the proapoptotic protein BID mediates mitochondrial damage induced by caspase-8, which is activated by the death receptor complex associated with the cell membrane (10). Yuan and her team additionally uncovered the essential role of caspase-11 in the activation of caspase-1 to promote inflammation and cell death (11). Caspase-11 is a critical mediator of pyroptosis, an

inflammatory form of cell death that most often occurs under pathological conditions (12).

Discovery of Regulated Necrosis

In 1993, Yuan was promoted to assistant professor of medicine at Harvard. The position ended three years later when she moved her laboratory to Harvard's Department of Cell Biology, where she became an assistant professor and, later, an associate professor and a full professor. Today, Yuan is Harvard's Elizabeth D. Hay Professor of Cell Biology.

In 2005, Yuan led a landmark study that identified a vertebrate-specific necrotic cell death mechanism that she named "necroptosis" (13). Unlike apoptosis, which was first discovered during genetic studies of *C. elegans*, necroptosis was revealed via small molecules identified from cell-based screens. The screens led to the discovery of necrostatin-1 (Nec-1) as a small-molecule inhibitor of necroptosis. Nec-1 has been widely used to characterize the role of necroptosis in human diseases.

Her findings overturned the traditional dogma that necrosis is only passive cell death, and opened the possibility of developing therapeutics for the treatment of diseases involving necrosis. For this and other pioneering discoveries concerning molecular mechanisms in the regulation of apoptosis and necroptosis, Yuan was elected as a fellow of the American Academy of Arts and Sciences (2007) and the American Association for the Advancement of Science (2017).

RIPK1: A Key Mediator of Inflammation and Necroptosis

While exploring the mechanism of Nec-1, Yuan and her team identified its target, RIPK1 (14). They additionally showed that two other necrostatins target RIPK1 in the necroptosis pathway. The team wrote that the "data establish RIPK1 as a new target for therapeutic drug development for human diseases involving necrotic tissue injury, and they establish necrostatins as first-in-class potent and selective inhibitors of RIPK1." Shortly thereafter, they identified a set of 432 genes, which are part of a cellular signaling network that regulates necroptosis (15).

Yuan and her colleagues next investigated RIPK1's theorized contribution to human neurodegenerative disorders (16–18). They noticed the signatures of activated RIPK1 in mouse models and human post-mortem pathological samples of multiple sclerosis, amyotrophic lateral sclerosis (ALS), and Alzheimer's disease. The studies demonstrated that inhibiting RIPK1 pharmacologically can help to reduce disease-related damage to central nervous system axons and neurons in animal models of neurodegeneration.

Link Between Aging and Neurodegeneration

Age is a known primary risk factor for nearly all neurodegenerative disorders, but the molecular link between aging and neurodegeneration has long eluded scientists. In 2018, Yuan and her team shed light on the connection by revealing that aging provides a sensitized background for RIPK1 activation in the central

nervous system (19). This background cooperates with genetic defects to allow activation of RIPK1 to promote the onset of neurodegeneration.

Yuan and her colleagues found that two protein kinases, TAK1 and TBK1, work together to suppress the activity of RIPK1. Yuan discovered that TAK1 expression declines after middle age in human brains. Deficiency of TBK1 is a major genetic risk factor for ALS and frontotemporal dementia. Thus, age-dependent reduction of TAK1 levels can cooperate with inherited TBK1 deficiency to promote the activation of RIPK1 kinase to mediate neuroinflammation and cell death. Yuan's finding may have broad implications for age-dependent neurodegenerative diseases because the sensitization of RIPK1 activation in aging brains could provide a potential general mechanism to promote the onset of a diverse set of age-related neurodegenerative diseases. It also predicts the potential therapeutic benefit of targeting RIPK1 for the treatment of such diseases.

Promising Drug Development

Yuan's IA reviews her team's discovery of necroptosis and RIPK1's role in this form of regulated cell death (20). She says, "We discovered the role of RIPK1 as a key mediator of the deleterious responses downstream of tumor necrosis factor receptor 1 (TNFR1) and found

RIPK1 to be an important pharmaceutical target for the treatment of human inflammatory and degenerative diseases. Small molecule inhibitors of the kinase have been advanced beyond Phase I human clinical trials for the treatment of ALS, Alzheimer's disease, rheumatoid arthritis, psoriasis and Crohn's disease."

Yuan and her colleagues hold numerous patents for necroptosis inhibitors. In 2015, she cofounded the San Diego-based biotechnology company Incro Pharmaceuticals, Inc., with a focus on the RIPK1 inhibitors. The company was acquired a year later by San Francisco-based Denali Therapeutics, Inc., where Yuan serves as a consultant. Denali recently formed a strategic partnership with Sanofi—valued close to \$1 billion—to codevelop RIPK1 inhibitors for the treatment of multiple human inflammatory and neurodegenerative diseases.

She says, "I am fortunate to work with a group of outstanding postdocs, students, and collaborators to dig ever deeper into the mechanisms of cell death. I am excited by the pharmaceutical industry's interest in our research. It is my hope that our discoveries eventually will be translated into new treatments for human diseases to help patients like those who inspired me to work on cell death mechanisms more than three decades ago."

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