PNAS PROFILE

Profile of Ana Maria Cuervo

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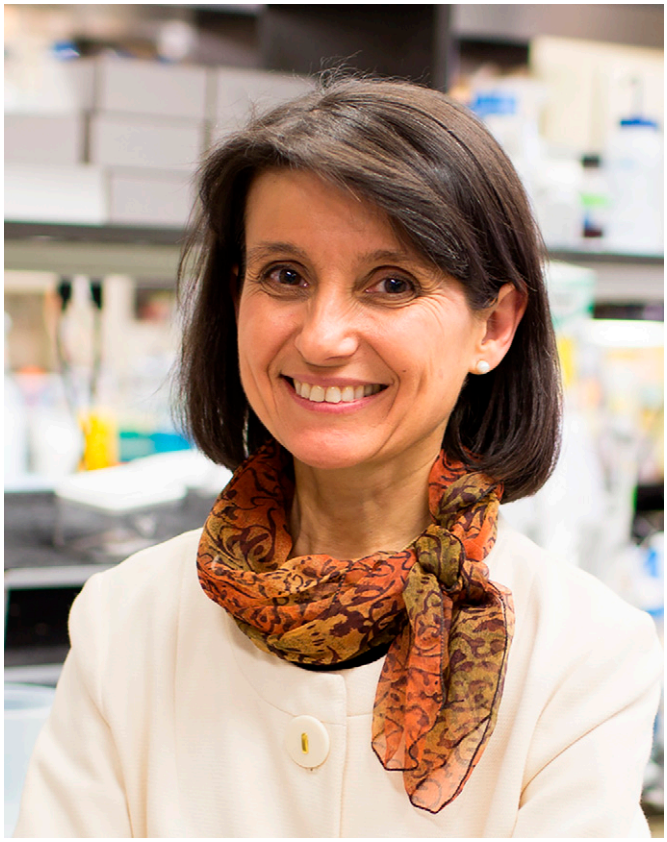
As a child, Ana Maria Cuervo wanted to be a mathematician. "I have to confess that I love numbers," she says. Because her parents were unsure whether one could make a living as a mathematician, she decided to go to medical school when it came time to choose a career. "I studied in Spain, where we have to decide our career when we are 17 years old," says Cuervo. "I always liked biology in general, but then I thought biomedicine was a better option because you can apply it to diseases," she says. When she eventually focused on biomedical research, Cuervo was able to harness her initial passion for mathematics as well. "Fortunately, science eventually brought me to numbers, too," she says.

Cuervo went on to decipher many of the molecular mechanisms by which proteins and organelles are recycled by lysosomes, cells' recycling factories, in a process known as autophagy. Her work showed that lysosomal degradation can be selective, and she has investigated how disruptions in this process contribute to aging and neurodegenerative and metabolic disorders. In her Inaugural Article, she describes how a reduction in a selective type of autophagy, chaperone-mediated autophagy (CMA), can affect atherosclerosis (1). Cuervo is now a professor in developmental and molecular biology and medicine and codirector of the Institute for Aging Studies at the Albert Einstein College of Medicine in New York City and was elected to the National Academy of Sciences in 2019.



Ana Maria Cuervo. Image credit: Jason Torres (photographer).

From Medicine to Research

Even as Cuervo began her medical studies at the University of Valencia in 1984, she knew she did not want to be a physician. "That was very clear in my mind, and I thought that by studying medicine, I [would] learn more about biology and physiology," she says. Studying medicine got her even more interested in researching the basic cellular and molecular processes underlying bodily functions. "When I learned about physiology, I was mesmerized by the complexity and precise regulation at the cellular level," says Cuervo.

At the time, it was uncommon in Spain for graduates in medicine to do research. "I really wanted to do research, and I was very lucky that in my second year of medical school I met a professor [who] had a small research lab," says Cuervo. She worked with Ximo Roma on various small research projects. "He was amazing in teaching us about the research process and the scientific method, on how you formulate a hypothesis and test it. It was just a completely different world for me," she says. "I was still going to the hospital because I had to, but basically my life was in the lab with the rats where we were studying nerve conduction."

The experience spurred Cuervo to join the PhD program in biochemistry and molecular biology at the University of Valencia in 1990, after she earned her MD degree. Cuervo decided to pursue an interest she had first developed in medical school. "Of all the clinical rotations that I did, the one that really impacted me was geriatrics," she says. "I wanted to learn about why we get old."

Cuervo decided to work with Erwin Knecht, who studied lysosomes. "Aging was not a glamorous field at that time," she says. "His way of explaining lysosomes was as garbage containers inside the cells that, as we age, fill up, and things start to go wrong," she says. "I was lucky that my interest in aging brought me to lysosomes and to such an amazing mentor."

During her doctorate, Cuervo also received a fellowship to work with Fred Dice at Tufts University over the summers. Her work on lysosomes benefitted from the close

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collaboration between both laboratories. "It showed the beauty of collaboration and was the best learning experience for a graduate student," she says. "We demonstrated that lysosomes can selectively choose what is going to be degraded."

It was an unexpected discovery. "At that time, everybody thought that lysosomes were garbage containers that cannot discriminate," says Cuervo. "I didn't know at that time that this was breaking dogma, and only followed the data," she says.

After finishing her doctorate in 1994, Cuervo continued her work on lysosomes as a postdoctoral researcher with Dice. During this time, they discovered a receptor in lysosomes, LAMP-2A (2). "That was the first receptor for the proteins selectively targeted by chaperones to lysosomes," she says. "Identifying this receptor was important, as it was key to proving that lysosomes were able to degrade proteins selectively and to start dissecting the lysosomal transport system of what we named chaperone-mediated autophagy, or CMA," says Cuervo (3).

Together with Dice, Cuervo also focused on aging, a direction she pursued when she started her own laboratory at the end of 2001 at the Albert Einstein College of Medicine.

Aging and Lysosomes

In her own laboratory, Cuervo delved into the workings of the LAMP-2A receptor and dissected components of CMA (4, 5). She also uncovered the physiological role of CMA in regulation of metabolism (6, 7), circadian rhythms (8), and stemness (9), and worked on the discovery of mechanisms of lysosomal selectivity, such as lipophagy (10), ciliophagy (11), and endosomal microautophagy (12). Cuervo credits the mentorship of Knecht and Dice, as well as the effort and initiative of researchers in her laboratory, for her success in characterizing lysosomes and autophagy. "It's really been a team effort," she says.

Cuervo also characterized CMA and its links to disease. "We [now] have many studies in animal models and in patients showing that the activity of CMA decreases with age and aggravates diseases of aging, such as neurodegenerative disease, metabolic disorders, and cancer," says Cuervo.

Cuervo's studies of lysosomes and aging also prompted her to investigate neurodegenerative diseases. "Neurodegeneration is an age-related disease, and we know that the lysosomal pathway gets worse with aging, so a big part of my lab is focused on the contribution of autophagy malfunctioning to neurodegenerative diseases," she says. "We showed the first connection between CMA and a human disease, when we found that in Parkinson's disease this type of lysosomal degradation goes down," says Cuervo (13).

Cuervo's work could pave the way toward treatments for neurodegeneration. "In a very recent paper we showed that if you block CMA in neurons, this gives you neurodegeneration, and we have now even developed molecules that can activate this pathway and see a beneficial effect in mouse models of Alzheimer's disease and of tauopathies," she says (14). Cuervo cautions that these studies are in mouse models, but she envisions this research moving to the clinic in the near future; companies have already started to work on some of the molecules she developed.

In addition to neurodegenerative diseases, Cuervo has also been studying the links between the lysosomal pathway and metabolic disorders.

Autophagy and Atherosclerosis

Selective lysosomal degradation by CMA is tightly linked to metabolism. "For example, we showed in vivo that if CMA goes down in liver, you develop a full metabolic syndrome," says Cuervo (6). "That led us into the area of metabolic disorders and motivated us to learn more about how this pathway contributes to glucose and lipid metabolism and what happens if it doesn't work," she says.

In her Inaugural Article (1), Cuervo found that a reduction in CMA can contribute to cardiovascular conditions, such as atherosclerosis. The project began from her interest in analyzing the vasculature of animal models without CMA.

"In the vasculature, CMA seems very important for those cells (macrophages and vascular smooth muscle cells) to protect themselves against proatherosclerotic diets, like the Western diet," she says. "We not only show that not having CMA makes organisms more prone to atherosclerosis, including data in patients, but also that if we prevent this age-related decline and maintain active CMA by expressing the LAMP-2 receptor in a transgenic mouse model, the mice are protected against atherosclerosis," says Cuervo.

The findings could have implications for understanding the mechanisms of aging as a risk factor for atherosclerosis. "When you look at atherosclerosis, one of the big risk factors in addition to diet is aging," says Cuervo. "A 20-year-old [individual] can be eating high-fat food every day without getting atherosclerosis, but if a 60-year-old [individual] abuses fats in the diet, [they are likely to get] atherosclerosis, suggesting that something is protecting you when you are young," she says.

Cuervo's results suggest that one of the protective factors is CMA. "As you get old, lysosomes and autophagy are not working as well, and it makes you more vulnerable to the same dietary challenge that might have been fine when you were 20," she says. "The major takeaway is that these lysosomal systems are very important for protection against any kind of dietary challenge that we have," says Cuervo.

The results also suggest that this pathway could provide a way to prevent age-related vulnerability to atherosclerosis. "We included this animal model in which we were feeding them the same unhealthy diet, and the only difference is that they have very good CMA because we increased expression of the LAMP-2 receptor," says Cuervo. "Just improving this pathway is enough for these animals to not develop the typical, big plaques because their vascular cells are better protected against lipids and also because CMA upregulation improves their lipid metabolism and reduces production of pro-inflammatory products to those detected in young animals" she says.

Based on this proof-of-concept, Cuervo hopes that drugs could be developed to preserve this autophagy

pathway. "Hopefully this will stimulate other labs and industry to look into other ways to preserve CMA function" she says.

Cuervo points out that aging is a multifactorial phenomenon and goes beyond lysosomes. That said, different drivers of aging also tend to be interconnected. "My mom always used to say, 'in a clean house, everything works better,'" says Cuervo. "When we are improving lysosomes, if you look at the mitochondria of those animals, they are better, and if you look at DNA damage, there is less, etc." she says. Cuervo suggests that exponential benefits against overall aging may be accrued simply by acting on a few key drivers of aging.

The potential applications of targeting the lysosomal pathway could even go beyond age-related diseases, to other areas such as cancer. "This is just the beginning, and I think that there is this momentum about autophagy physiology, now after 20 years characterizing it molecularly," says Cuervo. "We know enough now to start targeting it and to be able to restore function. I'm very optimistic about it."

The clinical applications of targeting lysosomes harks back to Cuervo's early years as a physician. "For me, it's very rewarding that you start working in lysosomes, [something] that you cannot even explain to your family, and then, all of a sudden, they see how this work could lead to treatments for diseases that affect our elders," says Cuervo.

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