Molecular Biology of the Cell
Vol. 12, 777–778, April 2001

Essay

What Mitochondria Have Told Me

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Submitted January 19, 2001; Revised January 19, 2001; Accepted February 21, 2001
Monitoring Editor: David Botstein

INTRODUCTION

One year ago I retired as a professor from the University of Basel, closed my laboratory, gave up my office at the Biozentrum, and decided to help prepare the Swiss research environment for the next generation of scientists. It was a risky decision, because I had done research all my adult life, had done it with great passion, and was not sure whether I would be strong enough to go "cold turkey."

One year is a long time to be out of research, and as I found myself dealing with university presidents, science administrators, and politicians, my old life quickly receded into the distance. When I received the wonderful message that the American Society of Cell Biology had awarded Walter Neupert and me its prestigious Wilson Medal, my first reaction was pure joy. But when I read on, the joy gave way to panic: I would have to give a lecture! But a lecture on what? I had stopped doing research and would have nothing new to tell. Also, I had resolved a long time ago to stop giving research talks as soon as I stopped doing research. I had always felt that research seminars by scientists who are out of research lack the emotional sparkle of ongoing discovery. So, what could I say that would interest you?

It occurred to me that, sooner or later, each of you would stop doing research. For most of you, this moment is still very far away, but for others the moment may be drawing close. How many of you have secretly wondered what your life in research would leave you with? What will be the legacy of all those battles, all those triumphs, and all those disappointments?

So let me tell you a few lessons I learned from my life-long research on mitochondria. Or, to use the spiritual parlance of Californian beaches, let me "share" with you what mitochondria have told me.

I grew up in Austria after the Second World War when that country was still a scientific desert. I had always wanted to become a biochemist, but my university did not offer courses on that topic and I was left with reading whatever reprints I could get hold of. After getting my PhD degree in chemistry in 1961, my reprint collection and I took off for a vacation in Greece, and there, on one of those magnificent beaches, I happened to come across a few papers by French and Australian scientists who had an incredible story. They wrote that yeast cells have granules that look like mitochondria; that these granules can change dramatically, or even disappear, as a result of strange mutations that are not inherited according to Mendel's laws; that they can also disappear when the yeast cells grow in the absence of oxygen, and that they come back again when the cells are exposed to air. How could this happen? How could structures just disappear and then reappear out of nothing? Then and there, I decided that I would try to find out. I joined the laboratory of the best Austrian biochemist I could find and went to work.

I soon found out that much of what these papers said was wrong and that yeast mitochondria never disappear. For example, when the cells are grown without oxygen gas, the mitochondria just lose their cytochromes and several other proteins and become more difficult to detect by electron microscopy. They become what I called promitochondria. Was I disappointed? Not at all! I could write a scientific paper that corrected these earlier claims. And by then I had run into lots of other puzzling questions and could not wait to go on.

Here, then, is the first lesson that mitochondria told me: when you start out in science, do not worry too much about where to begin. Young scientists always ask me about "the hot topic of the future." They want to pick the right wave that will carry them straight to Stockholm. I always tell them that I do not know the hot topic of the future and that they should distrust anyone who tells them otherwise. I advise them not to worry about the topic but to find out what really interests them, and then to join the best laboratory they can find.

To come to my second lesson, I must continue the story of my early years in Vienna. After I had found that mitochondria do not come and go but are permanent structures, I started to wonder how they get all their proteins. By that time it was already known that proteins are made on cytosolic ribosomes, that mitochondria have many different proteins, that mitochondria have two membrane barriers, and that these barriers do not let proteins diffuse across. I was still quite young at that time and still believed that nature always chooses the most rational solution. The most rational solution, it seemed to me, would be to make all mitochondrial proteins right inside the mitochondrion itself, so that there would be no need to import them from the cytoplasm. There were already some indications that mitochondria could make a few proteins, but the physiological meaning and even the reality of this phenomenon were not at all clear. I thought that if mitochondria could make their own proteins, they should also have their own DNA. We worked out exotic new methods for purifying yeast mitochondria and found indeed that these contained a small but constant amount of DNA. Added DNase would only digest this DNA after the mitochondrial membranes had been destroyed by a detergent. At the same time, and unknown to us in that age of "snail mail," the electron microscopists Margit and Sylvan Nass in the United States had found DNase-sensitive struc-

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tures in chicken mitochondria. Because we had used a biochemical approach, we could measure how much DNA there was in mitochondria. The result was a shock: there was not enough DNA to code for the many proteins we knew had to be there. Today we know that yeast mitochondria make only 8 stable proteins, and human mitochondria make only 13. My first hypothesis had essentially been wrong.

Although today's award is for my work on mitochondrial protein import, my participation in the discovery of mitochondrial DNA still is the discovery that means the most to me. It was prompted by a wrong hypothesis. By disproving this hypothesis, I not only advanced my own career, but also our knowledge on mitochondria. This is the second lesson that mitochondria have told me: do not try to prove your hypothesis; try to disprove it. At that time I had not read Karl Popper and did not know that he had said all that long before. How many of us follow his advice? Is it not the rule to defend one's own hypothesis to the last stand? Is it not true that anyone who challenges your hypothesis automatically becomes your enemy? Is it not true that this un-Popperish attitude has made science a battleground when it could be a playground where everybody has fun?

When we discovered mitochondrial DNA in the early 60s, this discovery seemed the epitome of "pure" basic research without any practical applications. Journalists often asked me why this discovery was important and what it might possibly be good for. I should have remembered what the British physicist Michael Faraday said to the Chancellor of the Exchequer after he had shown him that moving a magnet through a coil of wire would produce an electric current. When the Chancellor asked him about the practical value of this exotic phenomenon, Faraday replied: "One day, Sir, you may tax it." But I was not as clever as Faraday and usually left the journalists wondering why in the world the Austrian taxpayers should pay for my esoteric research. But today, 35 years later, mitochondrial DNA pops up everywhere: it helps us track criminals, identify familial, tribal, and even linguistic lineages, diagnose diseases, and understand aging. Mitochondrial DNA is a wonderful example of the value of long-term research. Today, holy wars are fought over the differences between basic research, applied research, mission-oriented research, and so on. To the general public, and even to us scientists, these terms are confusing and often do more harm than good. Again, my research on mitochondria has given me an answer, and that answer is as follows: the only real difference between basic and applied research is the time frame. Long-term research has a very broad goal, is risky, is difficult to predict, and should be a main obligation of universities and governments. Short-term research has a more clearly defined goal, is less risky, is easier to predict, and should be a main obligation of the private sector. It is really quite simple.

The fourth lesson mitochondria have taught me is about myself. When Altmann first described mitochondria more than a century ago, he thought they were foreign organisms that live inside other cells. As we biochemists began to isolate mitochondria and to study their properties, we firmly established them as integral parts of our cells. But today the pendulum has partly swung back toward Altmann's position. As we learned more about the mitochondrial genetic system, we were struck by its bacteria-like properties. This similarity, and many other observations, have given new credence to the old suspicion that mitochondria have evolved from free-living bacteria. I will never forget the reaction of my departmental colleagues in Vienna when I first presented this hypothesis at the end of one of my research seminars: half of them laughed, and the other half stared at me in disapproving silence. To this day, the memory of this moment is enough to make my hair stand up. But now there is no longer any reasonable doubt that the endosymbiont hypothesis is basically correct. The last skeptics may have been won over by the discovery of an ancient mitochondrial DNA in the freshwater protozoan *Reclinomonas americana*. The mitochondrial DNA of this organism is not only about four times bigger than our own, but contains about five times as many genes. Many of these genes are those that we would expect to find in an organism that tries to become an endosymbiont.

The origin of mitochondria from free-living bacteria is an impressive tribute to the inventiveness and unity of life on earth. It gives a new dimension to the concept of individuality and answers two age-old questions of humankind: "who am I?" and "where do I come from?" This is what mitochondria answer: you are an assembly of two different organisms that decided to live together 1.5 billion years ago. We know that this assembly is still evolving. Our nuclear genome contains many scattered fragments of mitochondrial genes. These inactive fragments are probably molecular footprints of puzzling evolutionary pressures, which continue to push for even tighter integration of the two partners, perhaps even for a complete loss of mitochondrial DNA. These two organisms, which *are* us, must still come to terms with each other, they are still trying to sort things out. Each of our cells is an ecological battleground. Mitochondria seem to be quick fighters because the mutational clock of their DNA ticks 10 times faster than that of nuclear DNA. We are not yet the final product.

These are just a few of the things that mitochondria have told me. Few human beings I have known have been as profound. What I have learned from my life in research now enriches me much more than I had imagined. In fact, this impact still grows as I now have more time to reflect on what I have found. Is this armchair science? It is indeed, but I do not see this term as derogatory. Today's science has become so busy, so competitive, and often so noisy that all of us should perhaps get an armchair and spend enough time in it, thinking about what we do. As mitochondria are now trying to tell their message to the next generation of scientists, they must do so against a much higher background noise. Those of us who help shape universities and research policies must do all we can to keep this background noise down. Noise is the enemy of science: every experiment is a conversation with nature, and we must be able to hear what nature tells us.