People & Ideas

Martin Hetzer: Taking the nuclear membrane beyond the barrier

Hetzer investigates how the nuclear envelope and nuclear pores organize chromatin and regulate gene expression.

The defining feature of every eukaryotic cell is the nuclear envelope—the double membrane separating the nucleus from the cytoplasm. Passage between these two compartments is controlled by the nuclear pore complexes that span the inner and outer nuclear membranes. But the last decade has seen a growing appreciation that the nuclear envelope and its pores do more than just control nucleocytoplasmic transport—they also regulate chromatin structure and gene expression in ways that have a major impact on human health and disease.

Martin Hetzer's research at the Salk Institute in San Diego, California has helped spur this reappraisal of the nuclear membrane. Hetzer began his scientific career studying catalytic RNAs (ribozymes) with Manfred Mueller at the University of Vienna (1). He was then introduced to the nuclear envelope as a postdoc with Iain Mattaj at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany (2). Hetzer set up his own group at the Salk Institute in 2004, studying the assembly of both the nuclear envelope (3) and nuclear pore complexes (4, 5). His lab demonstrated that a loss of pore integrity over time may contribute to aging and neurodegeneration (6) and showed that components of the pores can move into the nuclear interior to bind chromatin and regulate gene expression (7).

> "Now we look at the nuclear membrane as a major player in genome organization."

In a recent interview, Hetzer spoke about the changing view of the nuclear membrane and where he plans to push the envelope next.

EARLY ORIGINS

Where did you grow up?

I grew up in Vienna, Austria. I was very interested in science throughout high school. An early influence was Erwin Schrodinger's book, *What is Life?*, which is a question that continues to fascinate me. We still don't really understand how a cell works and what it is that makes this collection of molecules alive. In high school, I was particularly fascinated by the brain, but I didn't go into neuroscience because I felt the questions involved were too complex to understand in molecular terms. That's why I like cell biology, because you can address molecular questions in a living cell.

Why did you choose Manfred Mueller's lab for your PhD?

That was one of the hottest labs at the University of Vienna. They worked on autocatalytic RNAs, which at that time was a very active and exciting field. I was also intrigued by the whole idea of the RNA world and how life began. But what they worked on wasn't so important to me—I just wanted to learn how to do great science, and publish in top journals.

How did you find your way from ribozymes to the nuclear envelope?

I felt that the in vitro work I'd done during my PhD could only take me so far. I wanted to test my understanding of biochemistry in the context of a living cell. But I needed to find a lab where I could make a relatively smooth transition into cell biology. Iain Mattaj's lab at the EMBL in Heidelberg studied the nuclear envelope using cell-free systems—already a big step from purified RNA—but they worked with intact cells as well. I thought that would allow me to learn cell biology gradually. EMBL turned out to be a fantastic place for me, a very collaborative environment where people—not only from Iain's lab, but other groups too—taught me the basic techniques of cell biology.

MORE THAN A MEMBRANE

How has our view of the nuclear envelope and nuclear pores changed in recent years?

The nuclear envelope was discovered in the 1950s and for almost 50 years it was seen as a rather boring membrane that simply separated the nucleoplasm from the cytoplasm.

Then in 1999, a nuclear membrane protein called emerin was linked to Emery-Dreifuss muscular dystrophy. For many people, including myself, that was an eye-opener: that nuclear envelope proteins might regulate chromatin organization or gene regulation and could be relevant to disease. Now we look at the nuclear membrane as one of the major players in genome organization and gene expression.

It's the same with nuclear pores. Until the early 2000s, they were viewed only as transport channels, but over the last few years—and my lab has been a part of this—it's become clear that the nuclear pore has many other functions including, again, gene regulation. It was always assumed that genes regulated by pore proteins would have to be brought to the nuclear periphery. But we recently found that parts of the nuclear pore complex can move into the nucleus and regulate gene expression in the nuclear interior. So that expands the functional reach of this complex, and it has important implications for how pores really organize and regulate the genome.

Martin Hetzer

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The inverse is also true, because chromatin in turn helps organize the nuclear envelope…

That's right, and it's another interesting area that we explore. We've shown that the re-formation of the nuclear membrane at the end of mitosis is driven by nuclear membrane proteins that bind chromatin. So there's cross talk between the nuclear envelope and chromatin organization.

A very poorly understood aspect is the fact that the nuclear membrane and pore proteins change during differentiation. We now have some evidence that they actually drive differentiation. If that is really the case, then it makes sense that mislocalization or mutation of these proteins would cause pathologies like cancer, muscular dystrophy, or neuronal defects. Most nuclear membrane proteins remain uncharacterized, but every one that's been analyzed to date has been linked to a human disease—the list is now more than 30 different disorders.

How did you discover that the deterioration of nuclear pores over time might contribute to aging?

That was quite unexpected. One of our interests is how the nuclear pore assembles. The pore falls apart with the nuclear membrane in mitosis, and then re-forms at the end of it. Assembly also occurs during interphase to ensure that there are enough pore components for both daughter cells. But nobody knew what happens when a cell leaves the cell cycle and starts to differentiate. Does pore assembly still go on? If so, we'd expect to get an extremely high concentration of pores in the nuclear membrane over time, which wouldn't make much sense. Alternatively, the pores could turn over, but that was also hard to imagine because the pores are structural components of the nuclear membrane that span the inner and outer envelopes. It wasn't obvious how a cell would manage to disassemble this complex.

So we began to ask whether pore components important for the assembly process are still expressed in the post-mitotic cells of *C. elegans*. To our surprise, we found that they aren't expressed at all; they're completely shut down. We learned that all the pores of an adult worm are made early on in embryogenesis. That means that the structure is very long-lived—there are only a few other examples of proteins that last for the entire lifespan of a cell.

Then we wondered what happens to nuclear pores in cells that are extremely long-lived themselves, such as neurons, which can stay in a post-mitotic state for decades. We looked at neurons from young and old rats, and discovered that the nuclear pores deteriorate and lose their integrity over time. So from a very simple question, we ended up identifying something that might be relevant not only to aging, but also to neurodegenerative disease.

FUTURE DIRECTIONS

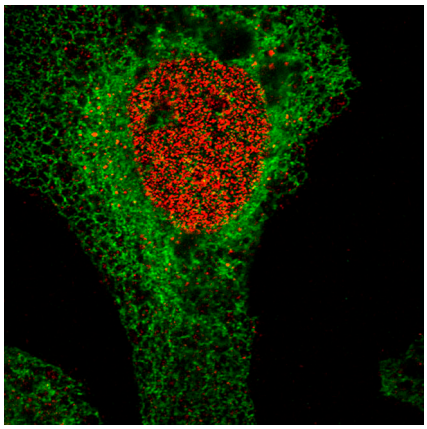
How might this loss of pore integrity contribute to aging and neurodegeneration?

The main function of nuclear pores is to keep proteins in the right compartment: cytoplasmic proteins in the cytoplasm and nuclear proteins in the nucleoplasm. When the pores deteriorate, these components mix. Tubulin, for example, can leak into the nucleus and form these long filaments, which might impair nuclear regulatory proteins and affect chromatin organization. You find similar tubulin filaments in the brains of Parkinson's patients, so now we're testing whether the deterioration of pores has a link to neurodegeneration.

Alternatively, when nuclear compartmentalization breaks down you could imagine a transcription factor that should remain in the cytoplasm entering the nucleus or a nuclear transcription factor leaking out. That would have a direct impact on gene expression and potentially contribute to aging.

What else is your lab working on at the moment?

We're trying to understand how nuclear pore complexes are involved in cell differentiation as well as aging. And we're beginning to perform genome-wide analyses that, in combination with our expertise in imaging, will help us understand how genes are organized in the three-dimensional space of the nucleus and how the nuclear membrane establishes and maintains this organization.



Nuclear pores (red) stud the nuclear envelope of a cancer cell.

We're continuing to work with different model organisms—we try to find the best experimental system to address each new question that comes up. Every system has its limitations, so I think you can analyze questions at a more sophisticated and interesting level if you don't limit yourself experimentally. I really enjoy bringing new expertise into the lab and developing new approaches.

What would you do if you weren't a scientist?

One thing I like about science is that it's a very interactive process requiring a lot of different skills. It's all about bringing together the best group of people and encouraging them to work on fascinating biological problems. I think that making movies would be quite similar in terms of developing a great story for a film and then bringing together a crew to make it. I also like the technological aspects of science such as developing and using advanced microscopy methods. Likewise, movie directors can push the envelope and incorporate new techniques in their productions.

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