Jürgen Roth: Immunogold master

Roth pioneered immunogold EM on thin sections and studies protein glycosylation.

Glycosylation, the synthesis of branched sugar chains on proteins, is a posttranslational modification commonly found on membrane and secretory proteins. Glycosylation is important for proper protein folding, and the composition of the sugar chains can also be used to track a glycoprotein's maturation.

When Jürgen Roth started working on glycoproteins, researchers had only recently begun probing the mechanisms and machinery of glycosylation using biochemical approaches. Roth applied his expertise in electron microscopy (EM) to develop methods for visualizing carbohydrates (1) and protein glycosylation. Using electron-dense colloidal gold particles covered with protein A to detect antibodies bound to thin sections by electron microscopy (2), Roth's seminal studies have shown where (3, 4) and why (5) protein glycosylation takes place. Yet there's still more work he wants to do, as we learned when we spoke with him recently at home on holiday in Switzerland.

CHILDHOOD IN THE WILD

I understand you grew up in East Germany…

Yes, that's right. Actually, I was born a year and a half before World War II ended, before the state of Thuringia was liberated by the American army and then left to the Russians. I grew up in what was initially the Russian military zone, which later became the German Democratic Republic.

What was it like growing up there?

Those initial postwar years—and many years afterwards—were difficult for everybody. It was a hard life. We were not poor, but we were struggling. But my memories are of a happy early childhood. My parents had to earn a living, so I was not really supervised all day. I grew up outdoors. I think for a young kid there's nothing nicer than to be in the forest or a field with friends.

Of course, when I was young, I did not understand the political situation in East Germany. Sometimes people—including an uncle of mine—would disappear for years and then come back and not speak about what happened to them. The eye-opener for me as a young boy was June 17, 1953: the first-ever uprising of the people against the Communist regime. I vividly remember the state of emergency. I was much older when they started to build the Wall in Berlin.

You first trained as a medical doctor…

Yes. I wished primarily to study biology, but there was simply no hope because of the very limited number of places. So I studied medicine because I hoped this would later give me a chance to do experiments like ones I had done in secondary school, such as dissecting an earthworm to look at the nervous system. It was very difficult to get into medical school; I was rejected from the university on my first try. But the following year I was admitted to study medicine at the Friedrich Schiller University in Jena.

After six years studying medicine, I became a resident in the Institute of Pathology at the University. I had purposefully chosen pathology because it is related on one side to clinical medicine and on the other side to experimental work. I was really lucky to join a research team lead by Professor Helmut W. Meyer, who was a microbiologist and electron microscopist. That's how I entered electron microscopy.

> "I was interested in the sweet aspect of membranes."

BARRIERS LIFTED

What sorts of techniques were you using?

Meyer's lab studied proteins and lipids in biological membranes using freeze-fracture EM. But I was interested in the sweet aspect of membranes, the carbohydrates at the cell surface, which are called the glycocalyx. At that time, there were some histochemical techniques for carbohydrates, but they were rather nonspecific. I stumbled onto some early work on plant lectins, proteins with carbohydrate-binding properties that had a much higher specificity. I obtained some concanavalin A from Wilhelm Bernhard in Villejuif, France, and later purified other lectins myself. Then we used peroxidase or ferritin to label the lectins. This gave us probes to detect specific oligosaccharide structures by electron microscopy.

PHOTO COURTESY OF JULIA VERENA ROTH

Jürgen Roth

How did you get out from behind the Berlin Wall?

In the early 1970s I had started to use particles of collodial gold as a highly electron-dense marker to label lectins. In this, I was following on from the work of Marc Horisberger in Switzerland, who was using lectin–gold complexes in scanning electron microscopy to study microbes. My publications on this caught the attention of Lelio Orci from the University of Geneva, who invited me to his institute to teach this technique to his lab.

At that time, I was living in East Germany, and I was a nobody. Ordinarily, there would have been no hope to follow this invitation, but the director of our Institute of Pathology, Professor Franz Bolck, was very supportive of me and the other PhDs.

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Text and Interview by Caitlin Sedwick
csedwick@gmail.com

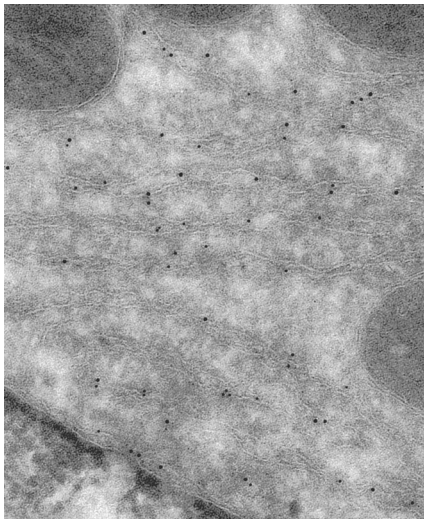

IMAGE COURTESY OF JÜRGEN ROTH

Immunogold labeling shows the location of the enzyme glucosyltransferase in the ER.

He also had a good contact with the Minister of Education. In 1976, I received a prestigious East German science prize, and, as he presented the award to me, the Minister of Education said, "Your travel to Geneva will be okay." So, I traveled to Orci's lab, and together we quickly generated a publication using ferritin-labeled lectins. He invited me for another visit, this time for a year. After that visit, I just stayed on in Geneva.

What did you work on there?

Before I came to Geneva, I used lectin–gold complexes to study the distribution and dynamics of glycoproteins on the cell surface. But this did not tell me anything I was really interested in. I wanted to know more about glycosylation as it occurs in the ER and the Golgi apparatus. I tried to get a more direct view of this using lectin–gold complexes to visualize carbohydrates and antibodies to detect glycosylation enzymes in the ER and Golgi on thin sections. Later on, the low-temperature resins developed in the lab of the late Eduard Kellenberger became very important for my work.

I had done some quite unsuccessful pilot experiments with antibodies and protein A–gold while I was still in Jena, but, on my second trip to Geneva, I met Moïse Bendayan, a postdoc in the lab. He had made a number of antibodies against exocrine pancreatic enzymes, so we joined forces. We used his antibodies, and I made a protein A–gold complex to specifically detect the antibodies bound to Epon thin sections. It worked! After incubating thin sections with antibodies against amylase and with protein A–gold, we saw gold particle labeling over the ER, the Golgi apparatus, and zymogen granules. This experiment was followed by many studies of other secretory, membrane, and cytosolic proteins. We also extended the stereology methods originally developed by Ewald Weibel, counting gold particles in our samples to achieve quantitative immunogold EM.

Had anyone done something similar?

Others had used gold-labeled reagents for cell-surface labeling. But we were the first to succeed at using protein A–gold on ultra-thin sections of tissues to visualize antibodies bound to antigenic sites exposed on the surface of the thin sections. This technique became the gold standard in immunoelectron microscopy.

"This technique became the gold standard in immunoelectron microscopy."

APPLICATIONS AND INVITATIONS

You have used this technique primarily to study protein glycosylation…

Yes, to study the cellular topology of protein N- and O-glycosylation. For example, we've looked at the subcompartmentalization of enzymes involved in these processes. Eric Berger and I were the first to directly demonstrate that the Golgi apparatus has distinct glycosylation compartments by localizing galactosyltransferase in trans-Golgi cisternae. I got the nickname "Mr. Compartment" because I worked so much on this subject.

Another interest of my lab was—and still is—the relationship between glycosylation and protein quality control. There is a very intimate relationship between protein glycosylation as it occurs in the ER and quality control of protein folding. For instance, we cloned an enzyme called glucosidase II, which trims glucose residues of oligosaccharides on proteins in the ER. Afterwards, we showed, together with Markus Aebi in Switzerland, that trimming of certain sugars routes incorrectly folded proteins from the ER lumen back to the cytosol for subsequent degradation. We've done extensive work on this and other components of the protein quality control machinery, which has resulted in the discovery of a novel vesicular ER exit pathway.

So you remain active in research?

After working at Geneva, I moved to the University of Basel and then to the University of Zurich. I became professor emeritus there in 2009. But in 2008 I had received an invitation from Jin-Won Cho at Yonsei University, Seoul, to become an international scholar in a special graduate research and educational program sponsored by the South Korean government. So, when I retired from Zurich, I came to South Korea. Now Professor Cho and I run a lab together, and my work focuses on how misfolded proteins are routed from the ER to the cytosol. The program ends after 2013, and then perhaps I will really retire to pursue some of my hobbies, such as hiking, skiing, and visiting museums. Or maybe I will just keep doing science.

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Roth and team members hike Mount Halla, a shield volcano in South Korea.

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