Cell

The Ongoing Shakeup in Organelle Biology

With the complexities of organelle communication and their dynamics under intense investigation, what are the new principles that are emerging, and where is the field headed? *Cell*'s Robert Kruger recently discussed these questions with Erika Holzbaur, Jennifer Lippincott-Schwartz, and Ivan Dikic. Annotated excerpts from this conversation are presented below, and the full conversation is available with the article online.

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Robert Kruger: For the past few days, I've been revisiting the things that I learned back in college and just thinking about the fact that of all the topics in biology the thing that seems most out-of-date right now is organelle biology. Even now, I'm carrying around in my pocket a representation of the cell on my keychain—the cross-section of the cell that's the standard textbook view. What do you think of this more old-fashioned model versus all the dynamics and interactions that we're seeing now. Is this useful, or what is it being replaced by?

Erika Holzbaur: I think just like we're not looking at pictures anymore, we're looking at video on every Facebook post. Jennifer's work, especially for me, was what transformed my view of the cell; watching her live-cell movies made me see everything in action, and realizing that the cell is constantly changing.

Jennifer Lippincott-Schwartz: I still think those models are really good, having some concept of the sub-compartmentalization because, in fact, cells are sub-compartmentalized into both membrane-bound compartments and membrane-less compartments that have functional read outs. But I think what's new over the last 5 to 7 years is that, in addition to the classic intercellular trafficking pathways that involves coat proteins and GTPases, we now are recognizing that there's a tremendous amount of inter-organelle contact-mediated trafficking of lipids and small molecules, of calcium, et cetera, and it's a whole other language that the cell is speaking, that we haven't understood.

RK: Do you think we have a whole sense of those hierarchy of interactions that are going on?

JL-S: No, no.

EH: No. None at all.

JL-S: It's unbelievable. It's almost equivalent [to] maybe 20 years ago, when we were first trying to understand intracellular vesicular pathways, the endocytic pathways, the secretory pathway, and how these organelles are communicating via vesicles. To a certain extent, we solved that problem, but what we're recognizing is that organelles are directly contacting each other and communicating that way, and we are just at the beginning of really understanding it.

Ivan Dikic: Quite a bit of the new stuff is dynamics, how things interact, how fast, how slow, and the quantitative aspects. I think today with this high-throughput [technology]—just look at CRISPR/Cas—this gives us an incredible amount of data, which can be used now in a quantitative manner, and biochemistry provides real direct protein-protein interactions, protein-lipid interactions; a lot of structural work is there. So, now the picture of a cell, which looked rather simple before, is very, very crowded. It's really exciting what biology brings us—complete visibility of atomic details to full organelles and how they communicate with each other.

EH: But to extend your point even more: it's not just biochemistry anymore but biophysics, that once we have these dynamics, you can really think about the forces that are causing these interactions to happen and to change over time.

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JL-S: I think part of what Erika is saying is that imaging has enabled different fields to suddenly come together at some level . . . . For many years, there [were] very separate fields of membrane traffic and cytoskeleton, and the two fields really did not communicate much. But now that we have the ability to visualize both the actin cytoskeleton at the same time that we're looking at membranes, we're suddenly having a much deeper, clearer vision of how these two systems are actually coupled and coordinating with each other. As Erika said, it's the language not only of chemistry that's entering into the picture, but it's the language of physics.

RK: So, if you're looking at the next 5 years, what do you think are the major areas of therapeutic interest that intersect with organelle or membrane or compartmentalization biology?

ID: Neurodegeneration is number one because it is a long-term pathogenic [process]. You need to have deficiencies that are not abrupt and in cancer or infectious diseases. In neurodegeneration, you have the defects in organelle dynamics, organelle diagenesis, organelle function that accumulates, and then you have signs of a disease developing in 10 years. There are a lot of different approaches. One approach would surely be increasing autophagy as a quality-control mechanism to deal with organelle deficiencies in a protective manner, but there are many others.

EH: But for me that illustrates a lot of the challenges going forward because we already know that we cannot just translate what we see in a simple cell model, like a cultured cell, like a HeLa cell, to a more complicated, highly differentiated cell, and that's just a cellular level. When you put that cell into context of supporting cells and neuron, and not just a neuron but glia and oligodendrocytes, that makes the problem more complicated, and I think we can't minimize those complications at this point. We have new tools and new ideas to answer these questions, but I also think we have to be careful about oversimplifying things, and I would challenge you: activating autophagy may not be the best way to cure a neurodegenerative disease. It might or it might not. We don't have the answers yet.

RK: Picking up that question of complexity: is it my imagination that for every cytoskeletal and membrane system organelle there's some interaction between each of them?

EH: [laughs] Yes.

RK: And I don't know if this is a good analogy, but I'm thinking about all the physiology that's going on in the human body between different organs and the communication between them. It's all multifaceted, multidimensional, and it's not exclusive. And, so—

ID: A lot is plastic. There's the message. Very, very plastic.

RK: How do you move forward? Do you build up to greater and greater complexity? Do you have to account for all of it?

ID: I think [we need] correlation between quantitative aspects, and correlation to [what is] functional, because everything in life has certain ratios and a certain degree. Nothing is black and white, so you need to reach the threshold where the function is relevant, and this is what we still miss in describing the cellular interior.

EH: I agree completely. It matters how fast it happens. It matters where it happens, and so by using those specifics, you can then tailor hopefully your therapy to a specific problem to fix this specific thing. I think the cancer cell field has really driven us with these ideas of specificity of attack.

RK: Going back to my keychain, the original model of the cell, what do you think, say 5, 10 years from now, of how we currently think about how things work, will [it] seem incomplete or potentially outdated?

JL-S: Oh, you mean wrong?

RK: I was looking for a more nuanced "wrong," I think.

ID: I think there is going to be an explosion of new discoveries but also reductionist views of functions. I think we are looking forward to a truly exciting next 10 years.

JL-S: I think we'll find that processes that we thought were fairly simple, like autophagy, which has particular cartoons, are going to be much more complicated, much more diverse in terms of the ways that it's occurring and that we may even have to devise new conceptual frameworks for how you describe it. I think people tend, once an organelle is defined, or a process is defined, to just think that this a given, when in fact all of what we're describing is our best effort to try to synthesize things, and as we learn more, that changes, and we need to be aware of that. We should not hold back on our ability to resynthesize things and re-conceptualize things to make it more coherent . . . .

I think the other thing that is potentially a conflict in terms of the way people are doing science, and the way that people are funding science, is that people come to particular questions with very different goals. On the one hand, somebody may come to a question because they want a cure for a disease. I'm going to study autophagy because I'm going to use it as a way to cure a disease, but there's also the more fundamental way of addressing biological issues, which is "I just want to understand how it's working," irrespective—at the most fundamental level—of how it might cure or not cure a disease, and I think both ways of doing science benefit our community . . . .

One thing that I want to bring up is that there's a huge excitement about proteomics and bioinformatics, and the assumption in that field is that somehow all you need to do is find the genes that are turned on or off and you're going to have the whole pathway. You're going to know what's happening. When in fact we don't have the foundational understanding of the way the cell is working, and so you have to have that research going on side-by-side with all of the bioinformatics.

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ID: Defining noise is the major challenge, because the noise is very large. This is something people don't really want to [do if] they don't work in interdisciplinary and critical settings.

RK: So what kind of noise are you talking about?

ID: Like in a mass spec screen when you have 1,000 proteins doing something, and then you start really evaluating it seriously in a quantitative manner. When did they show up? How [abundant are] these proteins, [and what is their] stoichiometry? These are small details that people ignore when they do big screens.

EH: One thing that was hitting me today was as a field we've been so focused on the proteins involved, and just a few of the talks are starting to think about the lipids and the lipid chains, and that's the big unknown, along with the metabolites. It's a whole other language of changes. Since we don't have good probes for them and it's difficult to answer that question, we'd rather do mass-spec screens, focusing on the proteins.

RK: Do you think the major story of all this is going to be told with those lipid movements and lipid dynamics?

EH: I think it's definitely part of it.

ID: It's difficult to say one or another; I think together it's better.

JL-S: I think one of the challenges is trying to understand: what is the cell trying to do in different situations? Fundamentally, the way I think about [it] is what the cell's trying to do is maintain a homeostasis, a metabolic homeostasis of some sort, which involves "big-time" metabolism. More and more people are recognizing this. Metabolism, which really was shoved to the wayside with the molecular biology revolution, is now coming back. People are beginning to start thinking hard about these fundamental cycles . . . the Krebs cycle, the glycolytic pathway, the pentose-phosphate pathway . . . .

EH: That brings up an interesting question: the cell's not trying to do it—the cell is amazing at doing it! So, when we talk about neurodegeneration, we're ignoring the fact that so many of these diseases are late onset, so even with these genetic mutations, you're making it into your 50s, 60s, 70s, 80s without disease, and that means a single cell is alive for that long a time.

RK: It's highly homeostatic.

EH: It's unbelievable, and those cells are a meter long. Yours are even longer. It's amazing how a cell could do that, so I think we have to give credit to this homeostasis, the many ways that a problem can be solved by the cell, the multiple different pathways that interact to get the job done. I think that's truly amazing, and if we can understand how it works, then we can better understand how it doesn't work.

JL-S: The other thing that I think possibly could become more mainstream is evolution—the evolution of eukaryotic cells and multicellular systems. That's something that people haven't been thinking about, but there are unbelievable relationships, and you can get very deep insights into why particular pathways are operating if you think evolutionarily because you see things aren't perfect. The cell is an evolutionary machine, in a sense. It has a history where— It's taking what it has at this moment and then modifying it in different ways, adapting to the environment, to the extent that we understand how that's played itself out and how different strategies have emerged depending on the particular multicellular system. It's going to give us some huge insights into not only how cells in complex cell systems are working but how you can impact them in terms of disease.

ID: Maybe I will just conclude for my side: I think all the challenges you heard now require a new type of training for new students and post-docs, because the challenges we [face] are very great, but they are also very much evolving. And I think our communities [should] do a lot to promote that with a proper education [that is] interdisciplinary, from evolution to medicine.