CSUN Department of Biology

BIOSPHERE

The Weekly Bulletin of Biology

Biology Colloquium: Friday, 11 September 2015, 2:00 pm in CR 5125

"Novel Dynamics and Regulation of Clathrin-coated Vesicle Formation at the Golgi"

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Add/Drop Now!

This is the last week to finalize your schedule. Thereafter, it will require special permission and a very compelling reason to drop a class.

Microbiology Student Association

The Microbiology Student Association will host a *Meet and Greet* from 10:00 am to 1:00 pm on Thursday and Friday (10–11 September) on the 2nd floor of Magnolia Hall. Food and drink will be provided, as well as an opportunity to meet MSA members.

New Developmental Geneticist

This semester we are welcoming two new tenure-track professors, hired after rigorous nationwide searches. In a later issue we will introduce the other newbie, Dr. **Cristian Ruiz Rueda**, a microbiologist. Here *Biosphere* presents an interview with Dr. **Mariano Loza Coll**, a developmental geneticist.

Biosphere: What research would you like to do in the near future?

Loza Coll: The genetics of stem cell regulation in fruit flies. The broad goal is to study conserved genetic pathways that do analogous things in other organisms.

B: When you say "stem cells in flies," what do you mean?

L C: When we think of stem cells in humans, we immediately think of the *embryonic* stem cells that can give rise to a new human. Flies don't have that. But they do have *adult* stem cells, which humans also have. These are cells in organs that replenishing other cells as they die, like the cells in your intestine. The degree of homology in those adult stem cells between flies and humans is astonishing—not only in their anatomical homology (where they are; what they do) and how they differentiate into different cell types, but also in the genetic pathways they use.

B: In humans and flies?

L C: Yes. It kind of makes sense; the common metazoan ancestor to protostomes and deuterostomes had a gut that had to somehow renew itself, so the genetic wiring of those adult stem cells stretches back through all the ancestors since then.

B: Every generation all the way back had to have a gut that renewed itself?

L C: Exactly. I think about that common ancestor a lot, that tiny worm that had a gut, gonads, a nervous system—all conserved. So, that's why we are studying the adult stem cells in a fly gut. And in their testes, too.

B: What do you do with these flies?

L C: What students would mostly do is use fluorescence microscopy to study these cells in their tissues, and the genes they express.

B: You look at the protein?

L C: We could, but we also look at the messenger RNA. Making a probe is super easy. We can make them in a week. Then we can ask how the expression of certain genes might relate to the function of these adult stem cells. What tells them to divide or stop dividing? What makes them make enterocytes versus enterendocrine cells in the gut, for instance?

B: How much training would students involved in this research need?

L C: Very little. It's conceptually simple. Anyone can construct a hypothesis of how genes communicate with one another in networks without getting into their biochemistry. And the manual work is easy; it can be learned in a few weeks. A good student would be ready after taking Genetics.

B: Are you recruiting students now?

L C: I've had students emailing me already. But I will need about 6 months to have the lab in full operation, so I didn't think it was fair to get them on board yet. Having said that, a big component of our work involves bioinformatics, and to do bioinformatics you don't need a lab, just a computer.

B: The lab work would pay off maybe after next summer? A student could get started in bioinformatics right away?

L C: Yes, yes. If someone doesn't need to get results right away, then they could work on the bioinformatics now, and do the lab work to test their models when the lab is up and running before next summer.

B: That's probably enough on your current work. Let's go back in time.

L C: My second postdoc was in the lab of Leanne Jones at the Salk Institute in La Jolla, but the whole lab moved to UCLA. The Jones Lab is interested in the same things I've been describing.

B: And you were specializing in…?

L C: My area was how genes connect to one another and form little networks and modules to control stem cells.

B: And what did you do before that?

L C: My first postdoc was at UCSD working with Jim Posakony. We were studying the genetic control of cells that undergo a series of asymmetric divisions. More specifically, we worked with cells that make external sensory organs, those "hairs," or "bristles," that cover the body of a fly. They develop

from precursors that divide a number of times asymmetrically. We wanted to know what makes two sister cells become different things (the shaft of the hair or the neuron that senses the movement, for instance).

B: What did you get out of that postdoc?

L C: I learned to think in terms of genetic networks and developmental states in the life of a cell. In terms of discovery, I characterized a gene that is highly expressed in the original precursor to the whole sensory organ. This led to several questions: What happens when you mutate it? Or if you take it out, or express too much of it? Where in the cell is the protein it encodes? When we mutated this highly expressed gene, most of the sensory hairs developed fine with very few malformed ones. I thought maybe the role of this gene is in preparing the cell for function down the road, not the moment when it is expressed. Maybe if the gene is not expressed, the fly's senses don't function quite right, but the immediate histological development seems mostly fine. The concept that stuck with me was how a gene can prime the system for something that is going to happen later in development. This could happen through a series of mechanisms. They may lead to modifications in histones that mark genes for later expression. Or another possibility, which I find fascinating, is that network states might interact with one another to regulate genetic expression. These networks exist in stable states. One or two genes may tweak to switch the network to an alternative state. In terms of stem cells, we need to consider the possibility that there are many things that are predetermined in regulation long before the stem cell divides and its derivatives differentiate.

B: A "maternal effect" would just be a special case of an egg, but it applies to all other cases too?

L C: That's right. So that postdoc training was very helpful for my thinking. Fast forward to the guts again: the stem cells in the gut make both enterocytes that absorb nutrients and enterendocrine cells that coordinate digestion. But that decision may be made by a stem cell even before it divides to give rise to either cell type. In fact, we have made mutations in gut stem cells that skewed the normal rates of enterocyte versus enteroendocrine differentiation.

B: Listening to you explain things, it strikes me that you are able to be much more of an *organ* biologist than if you were studying human cells in culture.

L C: Exactly. We are able to look at the behavior of stem cells *in vivo*, and how that impacts the function of the organs that they sustain.

B: Let's take another step back to your Ph.D.

L C: I was at the University of Toronto in the Department of Medical Biophysics.

B: So, just to note, the University of Toronto is the oldest of the world-class universities in Canada, and it has an illustrious history of biomedical discoveries.

L C: They would say that they are the largest and most venerable. The Department of Medical Biophysics claims to have been home to the

originators of radiation therapy. And U of T scientists discovered insulin earlier on. Nowadays, it's a huge and vibrant university that's connected to a lot of biotech companies, the government sector, and so on.

B: Okay, so at U of T…

L C: I was in the laboratory of Jorge Filmus, and we studied anoikis (which is Greek for "without a home"). It is the phenomenon whereby normal cells commit suicide if they become detached from the basement membrane to which they are normally attached. They undergo programmed cell death. We were studying gut epithelial cells from rats. A normal cell dies, but a cancer cell does not; and by resisting anoikis, it can metastasize. We took normal rat cells, introduced oncogenes, and cells that separated from the membrane did not die. The floater cells were fine, healthy, strong, which is mimicking what is happening in a cancer patient.

B: What is making the normal cells die?

L C: We don't fully know yet. But what we do know is that cancer cells are disregarding a normal adaptive evolutionary rule for a cell to die if it ends up detached. Hopefully by understanding these rules, doctors could use some kind of gene therapy to bring back the normal instructions.

B: What was the upshot of your dissertation?

L C: My favorite paper showed that the mutated oncogenes were not creating a special gain of function. They were just manipulating a normal timing mechanism. Normally, the cells don't kill themselves right away when detached. They can survive for about two hours after they detach. It's only afterwards that programmed cell death kicks in. I found that after you detach cells, a tyrosine kinase turns on right away and remains on for about an hour. This kinase would phosphorylate a bunch of proteins in the cell that collectively delay programed cell death. I found that these oncogenes are just prolonging that state of protection; they are not bringing anything *new* to the system. My hypothesis is that this window of protection has to do with allowing for cell division. When a cell divides it needs to be detached from the basement membrane for nearly an hour, and obviously needs to not die during that time! Cancer happens when those cells take on a permanent state of restraint.

Other published studies found that cells attached to a basement membrane have a physical tension that stretches the cells. Then some colleagues borrowed the idea of "tensegrity" from architecture—the notion that you can make a ridged structure if you have the right strings and some ridged rods. It became a popular form of sculpture. The idea, when applied to cells, is that when the cell detaches, all that tension is released. If this changes the state, we should not expect a gradual linear change in the state of the cell. It should be a nearly instant change. This spurred my interest. Genetic regulations are analogous in the sense that changes can spread in a network almost instantaneously.

B: Are you arguing that the tent thing is not what's going on because you have a two-hour delay?

L C: No, no. We think that the moment the cell detaches, all the pro-death mechanisms kick in. The earliest I could test was after 15 minutes, and we think that massive changes have already happened with all the pro-death machinery turned on, even though programmed cell death hasn't started. The amendment introduced by evolution is that there is protective restraint for an hour or so. If the cells are still detached, the restraint is lifted and programmed death proceeds.

B: So how did you end up in Toronto?

L C: I completed my undergrad degree at the University of Buenos Aires at a time when things were looking kind of bleak for science in Argentina. Some of us decided to try to go abroad.

B: Was it hard to get into such a prestigious University?

L C: To get some place like U of T, you need to do well on the TOEFL, you need to do well on the GRE, you have to have these credentials, etc. So it takes some going out of your way. We planned it for over a year, improving my English, re-learning all of Biology in English. I worked harder that year than any year since then.

B: Could you teach biology in Spanish?

L C: Now? I could, but it would take some effort. Back then we needed to decide whether to take the biology GRE or the biochemistry GRE. We all ended up taking the biochem one because the things in the biology GRE are all set up in plain English. We knew the biology better, but words like "shrub" might throw us off.

B: How does the undergrad curriculum differ between Argentina and the USA?

L C: The degree is longer, an extra year; six years, plus a research experience is required. There is also no such thing as G.E. All of our classes were science and math.

B: Well we're about done, but tell us about your life before college.

L C: I grew up in Buenos Aires. My parents were both medical doctors. (My mom still practices.) They never pushed me into science or medicine, but I guess the setting set my path. My interests were always around biology. Of course, they evolved as you can see during my postdocs and Ph.D. In fact, when I was a teenager I went around telling people I wanted to be an ethologist. Coming to CSUN where we have a department with all sorts of biologists is a little like coming home.

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