Yves Barral: Lessons from yeast on growth, renewal, and old age

Barral studies the regulation of cell growth and aging in yeast.

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Yves Barral

The many virtues of the venerable and humble budding yeast *Saccharomyces cerevisiae* are well known. For years it has served as a powerful model for studying the cellular processes that make us humans—its distant cousins—tick. But for all that study, *S. cerevisiae* is still surprising us with new lessons about ourselves.

In his laboratory at the Swiss Federal Institute of Technology in Zurich, Yves Barral is using *S. cerevisiae* to study fundamental aspects of cell biology. He's working on problems such as how septins help cells compartmentalize themselves when they divide (1, 2); how they designate inheritance of cell contents (3); and what these activities have to do with aging (4). Yeast can even teach us about learning and memory (5), as we discovered when we spoke with him recently.

L'ÉTRANGER

Do you have any strong memories from your childhood?

I was born in Mexico to parents who themselves grew up in the French colonies in northern Africa. When I was about two, we moved back to France, where we first lived in a small village in Normandy and then in Lyon. Probably because we were constantly moving, I was an observer from the very beginning. As a kid I always felt foreign, a little bit of an outsider, so I was not really involved in any particular sports or outdoor activities. I loved reading, drawing, painting, and observation.

My first intellectual passion was archaeology, but I realized at some point that I was not particularly good at learning all the languages one needs to be an archaeologist. When I was a teenager I developed a passion for philosophy. I built a pond in my parents' backyard, and in the springtime I spent hours at the side of the pond, watching what was taking place there and thinking about philosophy, until I realized that I was really a bad philosopher but that the frogs were very interesting. [Laughs] I think that's how I came to be interested in biology.

By the time you got to graduate school, you'd discovered an interest in yeast…

I started seriously studying biology at the École Normale Supérieure in Lyon. At first I was most interested in developmental biology because I thought it was fascinating how the cells of an organism organize themselves in space and time. But then I became convinced that most of the basic processes by which cells control their spatial organization are already extant in unicellular organisms. Multicellular organisms simply reuse things that were first discovered by simple unicellular organisms.

That's why I joined Carl Mann's lab to study the yeast cell cycle. I used to joke that *Saccharomyces cerevisiae* is actually a bicellular organism, with two different cells—the mother and the bud—with different specificities. One grows, the other supplies materials. So basically, budding yeast is the simplest multicellular organism in which to study development.

> "My feeling was that the phenotype was being taken too much at face value."

FIRST APPEARANCES CAN BE DECEIVING

You first studied septins as a postdoc in Michael Snyder's lab at Yale…

During the cell cycle, yeast switch from so-called apical growth, where the bud emerges and grows only from the apex, to isotropic growth. In isotropic growth, the bud grows throughout its entire surface but the mother doesn't grow. This intrigued me because it is not polarized growth; it's compartmentalized growth. How does a yeast cell know where the mother stops and the bud starts? The septins localize to the mother–bud boundary, so I started looking at them.

Septin mutants form very elongated buds because the cells keep growing from the apex. Others interpreted this to mean that septins play a role in redirecting growth to the entire surface of the bud. That's why, in the absence of septins, the bud grows from the tip. But that did not make sense to me because the septins are present only at the bud neck, not all around the surface of the bud. My feeling was that the phenotype was being taken too much at face value.

I noticed that this phenotype resembled that of many cell cycle mutants, and to me this suggested that septin mutants may actually have a cell cycle defect. The phenotype was not directly due to the lack of septins but more a consequence of how the cell reacts to the lack of septins: by trying to delay isotropic cell growth. And indeed, when I removed the checkpoint by removing the SWE1 kinase, allowing the activation of CDK, I observed that nuclear division took place much earlier and that the cells moved from apical bud growth to isotropic growth. However, this isotropic growth was not restricted to the buds. It also took place in the mother cell, which soaked up most of the material for growth, leaving tiny buds. That was what led me to postulate that the septins at the bud neck were actually there to form a boundary that ensures growth remains confined to the buds.

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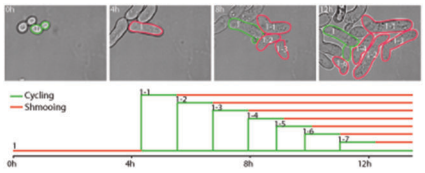

IMAGE COURTESY OF FABRICE CAUDRON

Budding yeast temporarily arrest the cell cycle to shmoo (bulge) toward a constant pheromone source. Cells that escape the arrest and bud will never shmoo to that pheromone again, but their daughters can.

Do septins form some kind of physical barrier to diffusion?

Yes. That's definitely the way I think of it now. At first we were only expecting to see such diffusion barriers in the plasma membrane, but we have also found evidence that septins limit diffusion within the ER and nuclear membranes. We think that the fence that is established in the ER depends both upon a protein called Bud6 and upon lipids. There is a specialized lipid domain at the bud neck that is involved in making the barrier.

AGING, THE PRICE OF MEMORY?

You've suggested that compartmentalization of the nuclear membrane affects cell aging…

In yeast there are DNA circles that pop out from the rDNA locus and contribute to aging. At every division, the mother cell retains these DNA circles. In one of our papers we proposed that, for retention to happen, DNA circles need to be associated in some way with the nuclear envelope. We also think this association needs to be with some factor that crosses both membranes of the nuclear envelope, because the diffusion barrier is specifically located in the outer membrane, and not in the inner membrane. Nuclear pores are good candidates, but there are potentially other candidates as well, and this is one problem we're studying right now.

Another thing I find intriguing about this is that cells segregate their chromosomes symmetrically but segregate these nonchromosomal DNA circles asymmetrically. That suggests that the cell is able to discriminate between the two, and it would be extremely interesting to know how that works. In general though, my lab would like to better understand what aging is all about. The dogma in the field is that aging is all about accumulating damage. But could it be that actually aging is more about accumulating memory? Perhaps aging is simply the price that we pay for the ability to individualize ourselves, and at some point we become so specialized that it begins to have many costs, particularly at the level of flexibility and repair.

The prediction would then be that any aging organism can accumulate memories, and we recently published a paper that was basically driven by this idea. We discovered that yeast mother cells are able to memorize missed chances at mating. Remarkably, this process of memorization takes place through protein aggregation, a known hallmark of aging, so that evidence of past encounters is retained in the mother cell during future asymmetric divisions.

> "Reality is frequently much more inventive than fiction. This should be embraced."

Yeast distribute many cellular components based on their age, including spindle pole bodies…

For a long time I have been interested in how the spindle is positioned within the bud neck. One of the interesting things that came out of our work on this subject was our discovery of the NoCut pathway, which prevents cytokinesis from happening before the chromosomes have cleared the spindle midzone. Before that, our work on spindle positioning showed that it is accomplished in part through interactions between astral microtubules and the septin ring at the bud neck. We became interested in how such interactions might occur.

At the time there were data showing that a protein called Kar9 was a microtubule capture factor residing at the bud cortex. We thought this meant it would not be involved in spindle positioning, so we started looking at Kar9 as a negative control. But it turned out that Kar9 was a terrible negative control because it was not at the bud cortex; it was at the tips of microtubules. And then we realized Kar9 was only on the microtubules emanating from the older spindle pole body, the one inherited by the bud. That was so striking to me that we have been working on how Kar9 localization is regulated ever since.

What is your favorite lesson you've taken from your work?

If there is one thing I have learned, it's that one should never take things at face value. Things are always much more interesting than they appear, even when they look very exciting. We all have the tendency to try to fit things in nice boxes or make nice stories, but reality rarely cooperates with us. Reality is frequently much more inventive than fiction. This should be embraced. It's what makes doing research so rewarding.

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The Barral lab at a retreat.