In praise of other model organisms

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The early cell biological literature is the resting place of false starts and lost opportunities. Though replete with multiple studies of diverse organisms, a few of which served as foundations for several fields, most were not pursued, abandoned largely for technical reasons that are no longer limiting. The time has come to revisit the old literature and to resurrect the organisms that are buried there, both to uncover new mechanisms and to marvel at the richness of the cellular world.

"Come back to us when you have demonstrated this in humans," said an editor to one of my postdocs presenting a poster at a recent conference. We use the protozoan parasite *Trypanosoma brucei* as a model to study Golgi duplication, and the implication was that the results of such studies are only worthy of a wider audience once they have been demonstrated in humans, or at least one of the other crown eukaryotes, that is, yeast, flies, worms, fish, or mice.

It was not always so. One only has to leaf through the early cell biological literature, from the fifties onwards, to appreciate the breadth of organisms under study. This is particularly true of *The Journal of Cell Biology* (or *The Journal of Biophysical and Biochemical Cytology*, as it was titled back then). The range was vast: from crickets to crabs, guinea pigs to grasshoppers, limpets to locusts, peas to pigeons, spiders to snails, and termites to turtles.

One reason for this, of course, was the invention of the electron microscope and its application to the biological sciences. Almost any cell or tissue could be fixed, embedded in plastic, and sectioned, and then viewed at a resolution far exceeding that of light microscopy, revealing subcellular architecture that had never before been seen.

Such studies not only attested to the validity of the cell theory, the basis of all known life on earth, but also showed that many cells were highly specialized, committing a large part of their metabolic energy to a particular cell function. Such studies identified model systems that could be used to pick apart a cell function into its component parts.

In my own field, membrane trafficking, the premier example was the pancreatic acinar cell from guinea pigs (Fig. 1), which is responsible for secreting (in a regulated fashion) those digestive enzymes needed after food digested in the stomach enters the small intestine. This cell devotes up to 70% of its total protein synthetic capacity to producing these enzymes. This meant that pulse-labeling with radioactive amino acids mostly labeled these enzymes.

Furthermore, this is an architecturally elegant cell, with the ER at the base (beneath and around the nucleus), the Golgi just above the nucleus, and the maturing secretory granules just above that, providing a clear map that could be used to plot the movement of newly synthesized enzymes (Fig. 1).

George Palade and colleagues exploited this architecture and EM autoradiography to show that these enzymes move from the ER to the Golgi to the granules, and hence to the apical plasma membrane, where they are released upon appropriate stimulation (Palade, 1975). They also fractionated these tissues at different times after pulse-labeling, purifying the individual organelles (using EM to confirm their identity) and showing that the enzymes (defined biochemically) took the same route as the one determined using EM. This was an elegant synthesis of biochemical and microscopic techniques that mapped the secretory pathway.

Biochemists were also quick to test a wide range of organisms for their studies, searching for those that would help them to dissect a particular cell function. Sometimes referred to as "zoo" screens, they would take any tissue, from any source (particularly slaughterhouses in my day), looking for that which gave the highest signal-to-noise ratio in their assay.

Another example from my field is protein sorting and the signals that direct cytoplasmically synthesized proteins to the ER. The assays devised by Günther Blobel and colleagues demanded ER microsomes that would transport the nascent secretory protein into the proteolytically inaccessible lumen (Blobel, 2000). A range of microsomes were tested but only dog microsomes proved efficient because, as it turned out, they had very low levels of RNases, which meant that the mRNA added to the assays to template the assembly of secretory proteins was not degraded.

Other examples from other fields include the mitotic kinase, CDK1, which was first characterized in the fission yeast *Schizosaccharomyces pombe*, then the poor cousin of baker's or budding yeast (*Saccharomyces cerevisiae*; Nurse, 2002); cyclins, which were characterized using sea urchins and *Xenopus*

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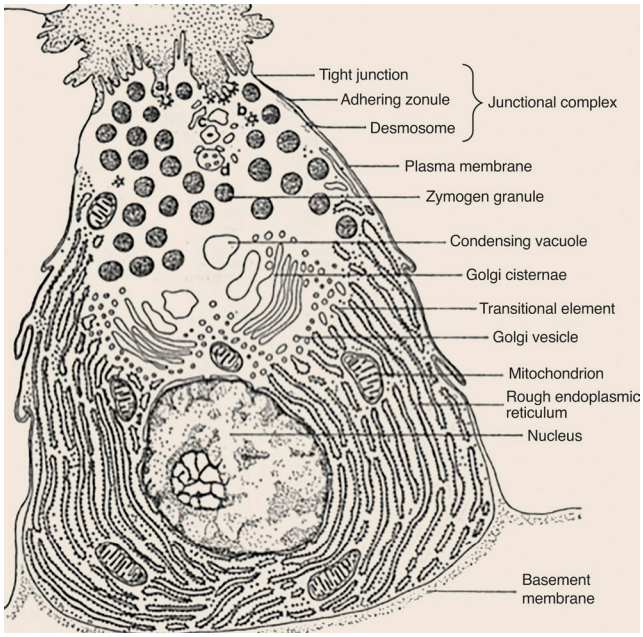

Figure 1. **Schematic representation of an acinar cell from guinea pig pancreas illustrating the architecture of this regulated secretory cell.** Adapted with permission from Case (1978) with permission from John Wiley & Sons, Inc., © The Cambridge Philosophical Society.

laevis oocyte extracts (Hunt, 2002); and telomerases, which were first characterized in *Tetrahymena thermophila* (Blackburn, 2010).

But the deeper one needed to look into cellular mechanisms, the narrower the range of organisms became. Biochemical methods, particularly fractionation, are often empirical and organism-dependent, requiring a considerable investment of time and energy. Electron microscopy has similar requirements, especially immuno-EM. Molecular biology tools were not then as sophisticated, and cloning and sequencing were very time consuming. Only by focusing on a few organisms was it possible to elucidate mechanisms at the molecular level within a realistic timeframe. Most work in the membrane trafficking field, for example, used budding yeast and mammalian cells as model systems.

But focus comes at a price, one being to ignore all the other organisms in the old literature, partly because it is so vast and time-consuming to explore, and partly because much of it is still inaccessible, particularly those journals that have yet to be converted to electronic formats. The days of wandering through libraries, picking up journals at random, and leafing through them is vanishing, in part because so much is available online. I think this is a shame because leafing through journals at random is easier (and more fun) than browsing online. In fact, for this piece I wandered, for the first time in many years, through the remains of our institute library, a rather forlorn place now, but still a far richer source when browsing for hidden gems.

But are there gems hidden in the seams of old literature that have yet to be exposed to the light of day? It is one thing to say that there are, and quite another matter to find them. I shall give just one example, as a form of encouragement, that there are systems manifesting fascinating cellular functions that cannot easily be explained using current knowledge. The example is chaetogenesis.

Chaetae are bristles made of chitin (a polymer of *N*-acetylglucosamine) and under-studied proteins, which together make them pliable, resilient, and tough. They occur in various invertebrate groups, and are prominent in annelids, where, among other functions, they serve for attachment to substrata and locomotion. Some chaetae look like hooks, others are serrated, and they can even adopt more complicated forms (Fig. 2).

But how are they made? If we go back 40 years, to a now unfortunately obscure paper on the mussel worm, *Nereis vexillosa* (O'Clair and Cloney, 1974), there are several clues. Electron microscopic images show that during chaetogenesis each chaeta is assembled in a multicellular factory, comprising a chaetoblast at the base of a funnel of follicle cells. Each chaetoblast has a patterned array of apical microvilli that secrete polymerizing chitin/protein complexes.

Microvilli appear and disappear at different times during chaeta formation (which takes ∼3 d), which suggests that they grow and shrink, alternating between secreting and nonsecreting phases, respectively. By coordinating groups of growing and shrinking microvilli over time one could imagine how complex chaetae could be manufactured. To make, for example, a serrated edge, growing microvilli would cast the tooth, then retract so that a space is generated. Repetition would generate a serrated edge (Fig. 2). Growing microvilli would likely secrete more chitin/protein polymers because of increased membrane surface area bearing the appropriate synthetic enzymes.

This biological system has all the hallmarks of a 3D printer, with the microvilli acting as the printing heads, assembling a complex structure through the selective addition of material in time and space. But what determines the patterned array of these microvilli and controls their temporal growth and shrinkage? Genetic programming is likely because the shapes of chaetae are highly stereotypical within a species, and therefore are often used for taxonomical classification. But what are the respective genetic factors, and what do these factors control? Answers to these questions could well lead to new insights into mechanisms that pattern the cytoskeleton.

When published in 1974, a mechanistic analysis at the molecular level must have seemed intractable, since this was even before the tools of molecular biology had been developed for general use. But now things are very different. Complete genome sequencing can take a matter of weeks rather than years. Deleting or mutating genes is also much easier, particularly with the recent introduction of the CRISPR/Cas9 technology.

For this particular example it should now be possible to do the most obvious and important experiment, which would be to fluorescently tag the microvilli (perhaps by tagging chitin synthase) and use high-resolution video microscopy to follow chaetogenesis, hopefully observing the growth and shrinkage of microvilli in real time. Such experiments would open up this whole area of biological 3D printing to molecular analysis.

So to go back to the comment at the beginning: what should one do? Should one tailor one's research question to the prevailing models? This is an obvious strategy, but fashions are fleeting and rooted (in the distant or forgotten past) in work with humble, often descriptive beginnings. So it seems to me to make far more sense to use whatever system can best answer

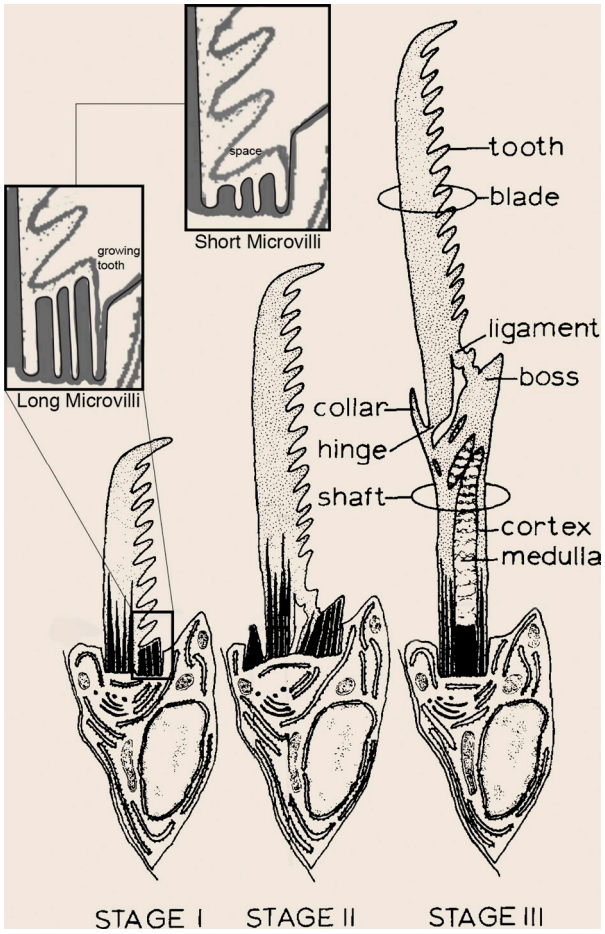

Figure 2. **Schematic representation of chaetogenesis in *Nereis vexillosa*.** The blade and teeth would be assembled at the apical surface of the chaetoblast, the distal part first, most likely by the secretion of chitin-protein polymers by microvilli (in black). One could imagine that growing teeth are cast by long microvilli (top left inset), which then retract (top middle inset), generating the intervening space. Repeated growth and shrinkage of microvilli would generate the serrated edge. Other structures (hinge, collar, ligament, and boss) would require more sophisticated programming of the microvillar array in space and time. Adapted with permission from Springer Science+Business Media (O'Clair and Cloney, 1974).

the questions that most fascinate you, even if it means straying beyond the confines of the crown eukaryotes. Such an approach requires passion, persistence, priority, publications, and presence. Passion is the curiosity aroused by a particular biological system or problem, the thing makes you get out of bed in the morning. Persistence is the drive needed to solve the problem. Priority is the ability to focus on a problem until it is solved. Publications are needed to disseminate your work, though the goal here is to publish work of the highest technical quality, not necessarily the most fashionable. Lastly, presence is needed, namely at meetings to interest others who might then want to share your goals. There are many other model organisms out there. One just needs the courage to seek them out.

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