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The Future of Cell Biology: Emerging Model Organisms

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Abstract

Most current research in cell biology uses just a handful of model systems including yeast, *Arabidopsis*, *Drosophila*, *C. elegans*, zebrafish, mouse, and cultured mammalian cells. And for good reason—for many biological questions, the best system for the question is likely to be found among these models. But in some cases, and particularly as the questions that engage scientists broaden, the best system for a question may be a little-studied organism. Modern research tools are facilitating a renaissance for unusual and interesting organisms as emerging model systems. As a result, we predict that an ever-expanding breadth of model systems may be a hallmark of future cell biology.

Reasons to turn to nontraditional models

The ends of chromosomes—the telomeres—have special powers to preserve chromosomes, the molecular basis for which was long unknown (Blackburn et al., 2006). What goes on at chromosome ends was famously first determined by exploiting a quirk of a nontraditional model organism, the ciliated protozoan *Tetrahymena*. Each *Tetrahymena* cell has a huge number of tiny, linear chromosomes—tens of thousands of them—and so each cell is far more enriched with telomere sequences than is a typical eukaryotic cell. In the late 1970's Liz Blackburn and Joe Gall decided to take advantage of this oddity, as well as the amenability of *Tetrahymena* to biochemical approaches and the newly-developed potential to sequence DNA, and discovered that telomeres in *Tetrahymena* minichromosomes contain dozens of CCCCAA repeats (Blackburn and Gall, 1978). Similarly repeating sequences were found later in diverse kingdoms of life, with the sequences acting as buffers at chromosome ends, which naturally degrade at each replication cycle (Blackburn et al., 2006). After Blackburn shared the Nobel prize for telomere work, she and her fellow Nobel Laureates stated about their discoveries, "Biology sometimes reveals its general principles through that which appears to be arcane and even bizarre." (Blackburn et al., 2006). Had telomere researchers restricted their focus to more popular genetic model systems, they

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might not have made the types of breakthrough findings that allowed us to now understand how chromosome ends are preserved.

Even researchers who cling to favorite genetic models can find reason to take risks with other organisms. Indeed, researchers have done so for as long as genetic model organisms have been in labs. Thomas Hunt Morgan, best known as the father of *Drosophila* genetics, worked on at least 50 other organisms as well (Sturtevant, 1959; Singer, 2016). And Morgan's appetite for diverse organisms apparently was not diminished by his group's successes with *Drosophila*. After the landmark *Drosophila* work was underway, Morgan turned to fiddler crabs to study how left-right body asymmetries develop, to protozoans to study regeneration, and to sea squirts to study how self-fertilization is prevented in animals that produce both sperm and eggs, to name just a few examples. Nearly every year, he produced one or more publications using organisms other than *Drosophila*. Many of the questions that Morgan asked with these other organisms could not have been addressed using *Drosophila*.

Morgan and his cell biologist contemporaries left behind writings packed with diverse biological questions (see for example Wilson, 1925; Morgan, 1934; Hörstadius, 1939). Only a fraction of these questions have been answered after decades of work with genetic model systems. If one reads cell biologist authors of that era, or if one follows his or her curiosity and thinks about fascinating questions from first principles, a very different landscape of ideas may emerge than does from reading modern cell biology textbooks—which necessarily focus mostly on the questions that have already been answered. There are a great many interesting and important questions to ask, which in many cases might best be answered outside of the popular model systems.

Recent research from our own laboratories has touched on just a few relevant examples: How can an animal cell survive complete desiccation? How did early animals evolve from single-celled organisms? What roles did interactions between kingdoms of life play in the origin of the animals? Attention has turned recently to the value of nontraditional model systems toward addressing diverse and interesting questions in cell biology (Sullivan, 2015; Gladfelter, 2015). Here, we argue that some of the biggest future discoveries in cell biology could come from the development and study of new and atypical model organisms.

New tools that can be applied to non-model systems

The good news to researchers who are tempted to try new paths is that some of our most important current tools will work in diverse organisms. For example, genome sequencing can rapidly yield meaningful answers to diverse questions, e.g. by producing a molecular parts list, helping to resolve an organism's place on the tree of life, revealing allele frequencies within populations, identifying loci under selection in lab-evolved strains, identify causative mutations in forward genetic screens—and more generally by providing a platform for future research on a little-studied organism. Genome sequence data also aids in other systems biology approaches such as protein identification from mass spectrometry experiments and chromatin immunoprecipitation sequencing experiments. Transcriptome sequencing now works with vanishingly small amounts of tissue, even from single cells,

making it possible to characterize transcripts present in specific cell types, at specific stages in an organism's life cycle, or under specific treatments (Liu and Trapnell, 2016; Hashimshony et al., 2016). The rapidly dropping costs of high-throughput genome and transcriptome sequencing mean that these methods increasingly can be applied to questions independent of immediate and obvious biomedical relevance.

Developmental biologists who ventured into studying evolution starting in the late 1980s benefited tremendously from a special set of antibodies that could recognize homologs of important transcription factors across diverse animals (Patel et al., 1989; Patel et al., 1994; Kelsh et al., 1994; Panganiban et al., 1995; Davis et al., 2001). The establishment of these reagents helped to demonstrate that anterior-posterior patterning in nearly all bilaterians is regulated in part by an ancient and conserved developmental regulatory network. Developing antibodies that specifically recognize homologous transcription factors in such diverse organisms was a challenge. However, many of the proteins that interest cell biologists (for example, cytoskeletal components and chromatin proteins) are highly conserved across diverse organisms and, as a result, are recognized by commercially available antibodies, allowing researchers to rapidly investigate overall cell architecture in any organism in which immunofluorescence works. The ease of using live stains, such as membrane dyes and the recently-developed fluorogenic probes SiR-tubulin and SiR-actin (Lukinavičius et al., 2014), means that it is possible to examine dynamic cell biological processes *in vivo* in diverse organisms. Moreover, the potential use of CRISPR-based technology to insert fluorescent tags into native loci holds promise for quickly and cheaply tagging any protein of interest *in vivo,* meaning that the explorer of new organisms does not need to focus solely on highly conserved proteins or processes.

Of course, for many biological questions, a method for disrupting gene functions is an essential tool. Efforts to bring mechanistic approaches to non-model organisms leaped forward with the discovery of RNA interference (RNAi), a broadly applicable approach for gene knockdown. However, RNAi has limitations, including the need to identify effective double-stranded RNA delivery methods that work well in any specific organism, the need to avoid off-target effects, and the need for extensive validation of the methods (Tenlen et al., 2013; Srivastava et al., 2014). Moreover, many organisms lack critical components of the RNAi pathway, and are thus not suited to this type of gene knockdown approach. Fortunately, recently developed CRISPR-based gene disruption approaches do not seem to require specific host machinery and may prove to be ideal for gene knockouts in diverse organisms. Moreover, CRISPR-based gene editing by homologous recombination allows for targeted changes to protein domains, meaning that the protein functions of emerging model organisms can be interrogated with the precision typically reserved for traditional models like worms and yeast. CRISPR methods may be a challenge for systems in which transgene expression has not yet been established, but DNA-free gene disruption using preassembled Cas9 protein and guide RNA gives hope, and has been shown to work in diverse systems including crustaceans, beetles, and even lettuce (Woo et al., 2015; Gilles et al., 2015; Martin et al., 2016).

Some questions cannot be answered using the popular genetic model systems

The ability to apply the above tools outside of traditional genetic models is important because in some cases, the best model for a question may not be a traditional genetic model. For example, how animal cells can survive extreme conditions can be studied using *C. elegans* dauer larvae, which survives drying (Erkut and Kurzchalia, 2015), but no animal is known to survive the extremes that tardigrades (Figure 1) can survive—including freezing to near absolute zero (Becquerel, 1950) and exposure to the vacuum of outer space (Jöhnsson et al., 2008; Rebecchi et al., 2009). How animal cells can survive such extremes is not yet well understood and can only be investigated by branching out from traditional modern organisms.

Stressed corals lose associated dinoflagellate algae that serve as important symbionts, a phenomenon known as coral bleaching, and this loss is exacerbated by rising ocean temperatures and pollution. This widespread biological phenomenon does not occur in traditional genetic model systems, leading some scientists to develop the anemone *Aiptasia* (Figure 1) as an emerging model system for an urgent problem (see Weis et al., 2008). *Aiptasia* can be raised in the lab, can lose symbionts upon heat shock, can be maintained with or without symbionts, and has a sequenced genome. The taming of *Aiptasia* has allowed cell biologists to start unraveling the molecular mechanisms that underlie bleaching in ways that would not be possible in other organisms (Gates et al., 1992; Weis et al., 2008; Baumgarten et al., 2015; Bieri et al., 2016).

Whole animal regeneration is another example in which emerging models provide key advantages. Certain genetic model animals, including zebrafish, can regenerate a subset of their tissues and organs after amputation or damage (Tanaka and Reddien, 2011; Gemberling et al., 2013). These regenerative powers, while remarkable, pale in comparison with those of animals like planaria, acoels, and hydra, which can regenerate any lost part. Cut these animals in half, for example, and each half can regenerate all of the lost parts (Tanaka and Reddien, 2011). How every cell type and tissue of an animal can regenerate, requiring dramatic organization of large parts of the body, and from little template, is a fascinating and incompletely understood question. Experiments in planarians (Figure 1) have revealed that regeneration is accomplished by multiple kinds of stem cells, at least some of which are pluripotent, and that Wnt and BMP signaling reestablish axes during regeneration (Elliott and Sánchez Alvarado, 2013; Roberts-Galbraith and Newmark, 2015). Acoels are flatworms that look a little like planaria (Figure 1) but that have been separated from planarians by at least 550 million years of evolution. Indeed, humans are more closely related to a planarian than an acoel is. Yet like planarians, acoels similarly use Wnt and BMP signaling for regeneration, suggesting the existence of ancient regeneration mechanisms that have been retained in certain branches of animals (Srivastava et al., 2014).

Some evolutionary cell biology questions specifically require the study of organisms at key places on the tree of life

When thinking about cell biological mechanisms, or indeed any biological phenomena, the quest to identify universal principles benefits from an understanding of evolutionary history. For example, membrane trafficking is solely a phenomenon of eukaryotic biology; investigating its origins provides a valuable complementary approach for identifying key regulatory mechanisms (Schlact et al., 2014; Richardson et al., 2015). The traditional model organisms are all members of a recently derived group sometimes referred to as the "crown eukaryotes" and provide only a narrow window into the evolution of membrane trafficking. By studying diverse but less well known single-celled eukaryotes such as the excavate *Naegleria gruberi,* the rhizarian *Bigelowiella natans*, and the cryptophyte *Guillardia theta,* it has become clear which membrane trafficking proteins are ancient within eukaryotes vs. those that have evolved more recently within specific lineages (Schlact et al., 2014).

Likewise, identifying universal principles by which cells interact within animals, and by which diverse animal cell types differentiate—from stem cells, to epithelia, to muscle cells and neurons—would benefit from an understanding of how animals first evolved. Insights into the cell biology of the first animals were stymied by the fact that traditional animal models are clustered within the Bilateria and hence too closely related to each other to reveal the cell biology of the first animals, while other models (e.g. yeast and *Arabidopsis*) are too distant evolutionarily. The key has been to study organisms based on their phylogenetic position and cellular attributes, rather than prioritizing their experimental tractability. Thus, the marriage of comparative genomic and cell biological approaches to the study of early branching animals such as sponges, ctenophores, and cnidaria, and the closest living relatives of animals, the choanoflagellates, filastereans, and ichthyosporeans, promises to help reveal the cell and organismal biology of unicellular and multicellular progenitors of all animals (Richter and King, 2013). This focus on evolution may also have implications for understanding modern animal cell biology. The hierarchical nature of animal tissue organization can complicate the study of animal cells and mechanisms underlying intercellular interactions. By studying choanoflagellates (Figure 1), which alternate between unicellular and simple multicellular forms, we may uncover ancient, core functions of pleiotropic animal proteins.

Challenges with starting new models, and some possible solutions

While the future is exciting for cell biology and the study of new model organisms, there are some challenges to keep in mind. To gain mechanistic insights into their cell biology, most new model organisms will need to be raised in or at least near the laboratory, and in many cases this can be a challenge. Weeds like *Arabidopsis* and pests like fruit flies were valuable early models for this reason—it was hard to not grow them. Marine organisms often share the convenience of a common growth medium, sea water, and historical work from marine labs has resulted in massive collections of wisdom about normal habitats, life cycles, and lab methods (see Morris et al., 1980 and Strathmann, 1987). Laboratories near the sea can benefit from local marine organisms. But most organisms, marine or not, do not easily

complete their life cycles in the laboratory. Even for those that do adapt fully to the laboratory, making husbandry for an organism work consistently can be a challenge. For this reason, starting with a wide variety of organisms that might suit a question and dabbling with raising them in the laboratory may help, as may talking to people with expertise in specific organisms' habits and life cycles.

Sydney Brenner, who founded modern *C. elegans* genetics research, preceded that work by playing with diverse bacteria, animals, and protists. Brenner grew a zoo of interesting organisms in the lab before visiting a nematology laboratory and narrowing his work to just one species of nematode (Brenner et al., 2001; Felix, 2008). That nematode was *C. briggsae*, rather than *C. elegans*. Brenner later switched to *C. elegans*, which grew better in the laboratory. Trying to culture organisms in the lab can be challenging but also fun as a side project. Brenner has said, "I just loved growing all these strange bacteria and other things!" about the dabbling he did while simultaneously working toward solving the genetic code in the 1960s (Brenner et al., 2001). Interestingly, the worm that Brenner initially set aside, *C. briggsae*, has recently grown in importance as cell and developmental biologists have started working on ever more diverse nematodes, exploring evolutionary questions that cannot be answered through the exclusive study of a single model, *C. elegans* (Gupta et al., 2007; Sommer and Streit, 2011; Félix and Barkoulas, 2012).

Our own experiences with emerging model systems involved narrowing from many species to few. One of us (NK) spent the first few months of her post-doc growing every choanoflagellate species she could and experimenting with different culture conditions. With time, as some choanoflagellate cultures died and some thrived in the laboratory, she focused on just two species, *M. brevicollis* and *S. rosetta*, which together offered a balance of experimental tractability and the opportunity to study relevant biology (namely, the evolutionary origins of multicellular development). Now, after more than a decade of studying and domesticating these two species, her laboratory has found that techniques developed for *M. brevicollis* and *S. rosetta* can be adapted easily to other choanoflagellate species. The other of us (BG) tried growing multiple tardigrade species before settling on some with desired characteristics including optically clear embryonic cells (Gabriel et al., 2007), and then among these species, choosing one for which there existed another laboratory starting to collect some early DNA sequence data (Daub et al., 2003). Fortuitously, an amateur tardigrade biologist Bob McNuff had already developed culture methods for this species, generously shared his methods (Gabriel et al., 2007). Many tardigrade species had been challenging to grow long-term in laboratories (Altiero and Rebecchi, 2001), and so the prior development of culture methods for one species was a crucial step toward continuing experimental work.

For organisms on which not many modern methods have been tested, choosing which techniques to attempt first, and which questions to settle first, can be bewildering. In our own experience, picking specific battles to fight and setting aside others was important; it allowed us to make some early progress without getting mired in possibly unsolvable problems or spreading efforts too thinly. Developing ways to make transgenic tardigrades seemed important, for example, but it took a back seat to developing a gene knockdown method and to answering long-unanswered questions that could be addressed with the tools

that we had already developed (Tenlen et al., 2013; Smith et al., 2016). Moreover, as we learned more about the biology of our study organisms, we were able to go back and overcome technical challenges that at first seemed insurmountable. Forward genetics in choanoflagellates, while clearly desirable, seemed unattainable until we discovered a sexual cycle in choanoflagellates and found ways to regulate it in the laboratory (Levin and King, 2013; Levin et al., 2014).

For us, there were pleasant flip sides to these challenges. For researchers starting work with a new organism, there is an opportunity to help set a healthy tone in a small, growing research community by sharing methods, data, and organisms. Some of the now-popular genetic model systems were founded as models with a similar spirit. For example, the early *Drosophila* geneticists set an important standard by sharing strains with each other, in large part to ensure that valuable strains were not lost (Kohler, 1994). Finding ways to draw colleagues and future collaborators into the study of an organism can be fun, and this may help in building the critical mass that can contribute to establish an organism as a new model. And in our experience, one of the treats of working with an organism that has been less studied has been that the work rewards staying open to surprises. The natural world is filled with fascinating phenomena, and one should not be surprised if he or she finds that by looking at an organism closely, he or she learns that it has additional, unexpected lessons to share.

Concluding remarks

While traditional model organisms continue to be powerful for many questions, we are entering an exciting era in the study of cell biology, one in which study organisms increasingly can be selected for their unique biological attributes rather than their historical experimental tractability. With this brief review, we covered just a few of the many ways in which diverse organisms are being probed for their answers to some of the most abiding biological mysteries. In the coming years, we look forward to seeing the suite of organisms studied by cell biologists expand as outstanding questions are addressed (see Outstanding Questions Box). We predict that the next generation of cell biologists will move nimbly from study organism to study organism, guided by scientific imperative rather than experimental expediency.

Outstanding questions

- What can organisms with extreme biology tell us about cellular and molecular mechanisms in ourselves?
- What new tools can be developed to facilitate research using potentially important but little-studied organisms?
- What is the molecular basis for direct cell-cell interactions between cells from diverse lineages, for example algae and fungi in lichens, or coral and dinoflagellates, or animals and their resident bacteria?
- How does global climate change impact on key cell biological processes, and vice versa?

- What can organisms at key places on the tree of life tell us about evolution and fundamental mechanisms in cell biology?
- What new discoveries as important as telomeres will derive from work on nontraditional model systems?

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Trends

- The tools used in cell biology are increasingly applicable to diverse organisms
- A great breadth of questions may be productively addressed using these tools
- Some questions cannot be answered using traditional model systems and so demand the development of nontraditional model systems

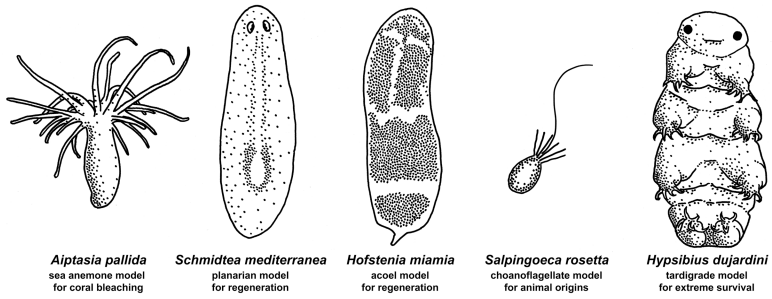

Figure 1.
Some of the emerging model organisms discussed.