COMMENT

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Evolutionary cell biology: Lessons from diversity

Novel perspectives emerge from a recent conference on the origins of eukaryotic cells, which covered phylogenetics, population genetics and evolutionary consequences of energy requirements and host–pathogen interactions.

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Witnessing the consolidation of a new field is an infrequent and exciting event. Such was the 'coming of age' of evolutionary cell biology at a recent conference on the origins of compartmentalized cells, held at the National Centre for Biological Sciences in Bangalore, India. From the conference program and accompanying discussion, it was apparent that a phylogenetic approach to cell biology is an informative and necessary tool for understanding molecular mechanisms of intracellular membrane organization and traffic, as well as cytoskeleton regulation. In fact, it would be ignorant and wasteful not to incorporate the large amount of comparative data emerging from genomic studies of diverse organisms into analysis of even the most fundamental cellular pathways.

As revealed at the conference, we can learn much from the search for the billion-year-old last eukaryotic common ancestor (LECA). What started as a quest to define how membrane compartmentalization arose in eukaryotic cells has generated an effort to find related pathways in prokaryotic cells, and has inspired studies of variant pathways in eukaryotes distinct from common model organisms. Thus, a notable benefit emerging from this reductionist exercise of defining LECA is the appreciation of diversity. For example, analysis of Rab protein function in *Tetrahymena* has revealed unique elaborations of their secretory pathway in response to their environment. Such variation shows how secretion can be naturally manipulated, with potential relevance for research or therapeutic development. Of more obvious medical relevance are membrane traffic proteins with restricted species distribution in mammals, including the primate-specific TBC1D3 and syntaxin 10, and CHC22 clathrin, which is present in humans and other vertebrates but not in mice. All three proteins have been shown to function in human cellular pathways that are directly relevant to type 2 diabetes.

At the opposite extreme, the identification by domain homology modelling of putative membrane coat proteins in the PVC (*Planctomycetes*, *Verrucomicrobia* and *Chlamydiae*) prokaryota genera supports the hypothesis that membrane coats comprising structural units of α-solenoids and β-propellers contributed to primordial membrane compartmentalization. Surprisingly, deep phylogenetic analysis of multiple proteins involved in membrane compartmentalization suggests that LECA was already a sophisticated eukaryote harbouring several membrane trafficking pathways. The emerging analytical approach of combining phylogenetics with structural motif identification has facilitated recognition of novel mammalian coat proteins of ancient origin, with links to neurological disease. Thus, in pursuit of the pure biological (and, indeed, historical) question of how compartmentalized cells arose, much of the acquired information has potential biomedical significance. Further insights are likely to arise as the field continues to address the complex relationship between energetics of cells, and the size, scale and organization of DNA and RNA in a eukaryotic cell. These considerations were discussed in the context of an unresolved issue: the origin of patently eubacterial components (for example, mitochondria and chloroplasts) in the modern eukaryote. This issue continues to pose a challenge for the reconstruction of evolutionary history using molecular-clock-based phylogenetic approaches.

A second point from the conference is how cell biological issues come into better focus when viewed through the micro-evolutionary lens of population genetics. Major changes in genomes and proteins can arise by non-selective random genetic drift. Furthermore, selection driven by host–pathogen interaction can leave functional traces in cells. Encounters with viruses and bacteria induce signatures of rapidly co-evolving host cellular proteins, wielding a considerable evolutionary influence. Moreover, searching for these pathogen-driven evolutionary signatures to characterize cellular evolution could have practical value for human infection and reveal targets for therapeutic intervention.

The conference also provided a forum for immunologists, a community that has long grappled with co-evolution, to contribute to discussions of evolutionary cell biology. Host–pathogen interactions shape immune system mechanisms, generating considerable phylogenetic diversity of immune response pathways, as well as rapid evolution of these responses in a species. For example, the receptors on natural killer cells (lymphocytes involved in the innate immune response) have completely different structures in humans and mice, and display major variation between humans and other primates. Population studies, as well as phylogenetics, reveal pathogen-related selective pressures driving receptor (and ligand) diversity. Sophisticated analytical methods for genome comparison, homologue and paralogue identification, and comparative population genetics have emerged from such immunology studies. Evolutionary cell biology can certainly benefit from the application of such methods.

In summary, the emergence of evolutionary cell biology as a significant field opens a new window on cell biology that arises from the analysis and appreciation of organismal diversity. In a satisfying example of 'turnabout as fair play', this new field will profit from genetic approaches that were developed in immunology, a field that has previously benefited greatly from contributions of basic cell biology. Evolutionary cell biology was inspired by the fundamental biological questions of how and why eukaryotic cells acquired endomembrane systems that enabled their interaction with changing environments and cooperation into multicellular organisms and tissues. However, such studies also have clear significance to human health. Understanding how the elegant adaptive responses of evolution have solved unique biological problems in diverse organisms (including humans) can be applied to manipulating human physiological pathways, as well as to establishing the mechanisms through which eukaryotic cellular complexity arose.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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