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Evolutionary origins and specialisation of membrane transport

Joel B Dacks[1] and Mark C Field[2]

From unicellular protists to the largest megafauna and flora, all eukaryotes depend upon the organelles and processes of the intracellular membrane trafficking system. Well-defined machinery selectively packages and delivers material between endomembrane organelles and imports and exports material from the cell surface. This process underlies intracellular compartmentalization and facilitates myriad processes that define eukaryotic biology. Membrane trafficking is a landmark in the origins of the eukaryotic cell and recent work has begun to unravel how the revolution in cellular structure occurred.

Addresses
[1] Department of Cell Biology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta T6G 2H7, Canada
[2] School of Life Sciences, University of Dundee, Dundee DD1 5EH, UK

Corresponding author: Field, Mark C (mfield@mac.com)

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The sophisticated last eukaryotic common ancestor

Many studies of membrane trafficking evolution focused on determining the organelles and proteins present in the last eukaryotic common ancestor (LECA), a hypothetical organism living ~10^9 years ago. As discussed in detail elsewhere [1,2], the numbers of predicted transport pathways and/or components within the LECA likely exceeded many extant organisms and LECA possessed all the canonical endomembrane organelles [1], extending to a *cis*, medial and *trans*-cisternal differentiated Golgi complex [3•]. These inferences also provide insights into the basic mechanisms of vesicle formation and fusion [1].

LECA is deduced to have possessed at least nine distinct vesicle coat complexes (including clathrin/AP1-5, COPI, TSET, COPII, retromer, ESCRT), ARF/ARF-like GTPases and their regulators [1,2]. LECA also possessed complex fusion machinery, including an extensive SNARE complement [4••], multisubunit tethering complexes [5], Rab GTPases [6–8] and regulatory factors [9]. Thus, LECA was capable of endocytosis, secretion and complex sorting, and while this is perhaps surprising, metabolism, cytoskeleton, mitochondrial functions, nuclear transport and many other cellular systems demonstrate similar predicted complexity.

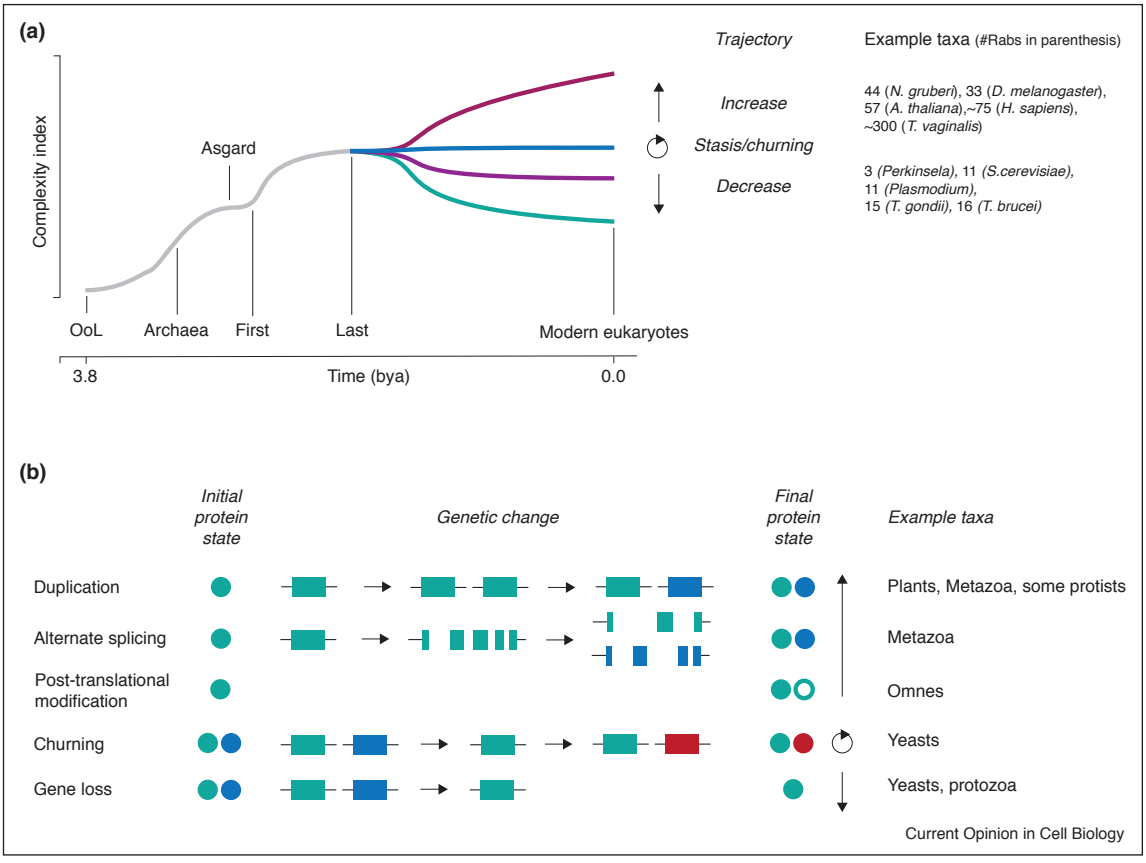
As new components and pathways are discovered within transport and sorting machinery, their relevance to LECA and subsequent evolution can be addressed, for example recent descriptions of vesicle formation machinery such as TSET [10], Tepsin [11,12•], TSSC1 [13•] and novel clathrin adaptors [14•]. As a complex LECA should now be taken as a starting assumption, within trafficking systems and elsewhere, this complexity leads to two questions; what preceded LECA and how has subsequent evolution unfolded?

How did complex membrane trafficking evolve?

The most basic evolutionary question, how did an endomembrane system originate, cannot be resolved by reconstructing LECA, as this represents an already advanced cell. As we assume complexity arose from a simpler state, this implies that transition from the first eukaryotic common ancestor (FECA; the first differentiated lineage from archaea giving rise only to organisms possessing some eukaryotic traits) to LECA required a revolution in cellular mechanisms (Figure 1). Promisingly, details of this revolution are now being discerned [15].

The basic vesicle trafficking machinery involves several protein families, each member of which functions at a specific organelle or transport pathway. Furthermore, organelle and pathway identity arises via combinatorial protein–protein interactions [16]. Different combinations of Rabs, SNAREs and tether complexes interact and substituting one or a few components can alter intracellular localisation. As these families evolved via gene duplication (and subsequent neofunctionalisation (Figure 1)), a mechanism for organelle evolution can be proposed; that organelle complexity arose where a primordial set of vesicle formation and fusion proteins allowed for transport and, through gene duplications and co-evolution of interacting proteins, developed new specificity. One pathway became two, and by simple iteration, many. This mechanism, the 'organelle paralogy hypothesis', found experimental support and has been elaborated upon repeatedly since the original proposal [2,9,17•,18,19•,20,21].

Figure 1



Generation of complexity. **(Panel a)** Timeline for alterations to complexity with cells and genomes across the history of life, with emphasis on the eukaryotic lineage. The 'Complexity Index' is an abstract concept to express compartmental sophistication, and is assumed to have increased during the ascent of eukaryotes (gray line), including the contributions from the archaea and bacterial (not shown) donors. Significantly, there are examples of extant taxa where the number of compartments, as predicted by the size of the Rab gene cohort, have increased (red), decreased (purple, teal) or remained approximately constant (blue) from the predicted state in the LECA. OoL; Origin of life. Note that points of complexity increase, as well as the curve topology, are arbitrary and for illustrative purposes; the true topology is unknown. **(Panel b)** Mechanisms for the generation of molecular complexity, based on examples from Rab protein evolution. Proteins are shown as circles, and genes as rectangles. The open circle denotes a modified protein, for example phosphorylated or acetylated.

An important corollary to the concept of trafficking complexity emerging via incremental steps based on gene duplications is that, if the order of these steps can be resolved, the order in which the pathways originated would emerge. While significant challenges remain, over two-thirds of predicted LECA Rabs fall into either an endocytic or broadly secretory grouping [7]. Adaptins can be resolved to allow inference of multiple independent origins of pathways for internalization from the cell surface and post-Golgi transport [10]. Similar information for any membrane trafficking protein can, theoretically, determine the order of organelle origins, presently an exciting prospect.

While adaptin complex genes are easily identifiable, a deep connection is also likely present between many additional coat proteins. Homology here is based on retention of one or more β-propellers followed by an α-solenoid, a 'protocoatomer' configuration, and members can be grouped into two subfamilies, with distinct structural features (Figure 2). Importantly this encompasses more complexes than classic coat proteins and includes the nuclear pore and SEA complexes and intraflagellar transport system, uniting the origins of most nonendosymbiotic organelles [22••]. Reconstructing the evolutionary relationships remains a tremendous challenge due to massive sequence divergence and recent attempts have provided only partial solutions (e.g. [23•]). Further, the NPC may contain multiple protocoatomer subfamily architectures, suggesting an origin post-dating establishment of several organelles [24,25,26•].

There are relatively few hypotheses for membrane trafficking's ultimate origin, and most are part of models