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Opinion

Bacterial Vesicle Secretion and the Evolutionary Origin of the Eukaryotic Endomembrane System

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Eukaryotes possess an elaborate endomembrane system with endoplasmic reticulum, nucleus, Golgi, lysosomes, peroxisomes, autophagosomes, and dynamic vesicle traffic. Theories addressing the evolutionary origin of eukaryotic endomembranes have overlooked the outer membrane vesicles (OMVs) that bacteria, archaea, and mitochondria secrete into their surroundings. We propose that the eukaryotic endomembrane system originated from bacterial OMVs released by the mitochondrial ancestor within the cytosol of its archaeal host at eukaryote origin. Confined within the host's cytosol, OMVs accumulated naturally, fusing either with each other or with the host's plasma membrane. This matched the host's archaeal secretory pathway for cotranslational protein insertion with outward bound mitochondrial-derived vesicles consisting of bacterial lipids, forging a primordial, secretory endoplasmic reticulum as the cornerstone of the eukaryotic endomembrane system.

Eukaryogenesis: A Matter of Compartmentalisation

Among the many traits that distinguish eukaryotic from prokaryotic cells, none is more conspicuous or significant than the eukaryotic **endomembrane system** (see Glossary). Like other eukaryotic-specific traits, such as mitosis and sex, its evolutionary origin remains obscure. The compartments of the endomembrane system are present throughout the major eukaryotic groups, as are the proteins that are specific to them [1]. Hence both were present in the eukaryote common ancestor [2], for which reason thoughts on the origin of the endomembrane system are linked to thoughts on the origin of eukaryotes themselves.

Despite many differences in their mechanistic details, theories for the origin of the endomembrane system traditionally derive it from inward invaginations of the plasma membrane, such that the endoplasmic reticulum (ER) lumen is topologically homologous to the environment [1,3–6]. This is true for theories that posit autogenous (nonsymbiotic) eukaryote origins [7] and for theories that posit eukaryotes to descend from symbiotic associations of prokaryotes [8]. Though most current theories now posit that mitochondria arose in an archaeal host through endosymbiosis (Box 1), the question of how the merger of two prokaryotic cells gave rise to a cell possessing a eukaryotic endomembrane system with elaborate vesicle trafficking (Figure 1) remains unanswered, as does the question of how **archaeal lipids** of the host's plasma membrane came to be replaced by bacterial lipids.

Though prokaryotes do not generate intracellular vesicle traffic of the kind found in eukaryotes, they do indeed generate OMVs, but these are secreted outwardly into the environment, not

Trends

Eukaryogenesis models struggle with explaining the origin of the endomembrane system and the transition from an archaeal plasma membrane based on isoprene ethers to a bacterial-type membrane based on fatty acid esters.

Bacteria and archaea secrete outer menbrane vesicles (OMVs) into their surroundings. If the endosymbiont that became the mitochondrion did so in the archaeal host, it physically generated the first vesicles of the endomembrane system.

Endosymbiont OMVs could only accumulate in the host's cytosol – fusion with each other could have generated compartments, fusion with the archaeal plasma membrane could have converted its chemical composition.

Starting endomembrane origin with outward flux of endosymbiont-derived OMVs integrates mitochondria, their lipids, and their energetics into current models of eukaryote origin, explaining why eukaryotes had a mitochondrion-bearing ancestor.

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Box 1. Endosymbiosis at Eukaryote Origin

The origin of eukaryotes hinges upon endosymbiosis, and eukaryotic cell complexity arose in the wake of mitochondrial origin, not as its prerequisite [57]. From the genomic standpoint a consensus is emerging that the origin of eukaryotes involved only two distinct partners: an archaeal host cell and an α-proteobacterial endosymbiont that became the mitochondrion [29,43,44,57,71,74–76]. This consensus does not touch upon whether the archaeal host bore a nucleus or not, but several issues require consideration concerning this discrepancy. It concerns, in particular, the purpose of a nucleus in an archaeal cell with cotranscriptional translation that remains unanswered in gradual models for eukaryogenesis that place the origin of the nucleus before that of the mitochondrion.

The selective pressures that brought forth the possession of the nuclear envelope (NE) as a permanent fixture of eukaryotic cells are, we suggest, distinct from the OMV-dependent ER origin of the NE itself. The presence of spliceosomes in the eukaryote common ancestor suggests that the initial selective advantage of possessing an NE was the spatiotemporal separation of spliceosomal splicing from translation, with spliceosomal introns stemming from group II introns acquired via endosymbiotic gene transfer from the mitochondrial symbiont [77]. Spliceosomal splicing requires a nucleus to exclude active ribosomes from intron-containing transcripts, because ribosomes operate much more rapidly than spliceosomes, such that cotranscriptional translation on nascent transcripts bearing spliceosomal introns would lead to defective polypeptides only. The physical exclusion of ribosomes from active chromatin via membranes would allow the slow process of splicing to go to completion before translation sets in. Similar to the intron hypothesis for the origin of the nucleus [77], our present suggestion for the origin of the endomembrane system requires a non-nucleated archaeal host with cotranscriptional translation at the origin of mitochondria.

inwardly into the cytosol. Decades ago, microbiologists observed that Gram-negative bacteria can secrete lipopolysaccharide (LPS) complexes [9] that presumably stem from the outer membrane [10] into the environment. As explained in the next section, quite a bit is now known about prokaryotic OMVs, but less about the proteins involved, which are, in some cases, homologous to those germane to vesicle scission into eukaryotic **multivesicular bodies (MVBs)** for example. Moreover, even mitochondria themselves are known to secrete **mitochondria-derived vesicles** (MDVs; Figure 1) into the cytosol [11–14]. No previous theory for the origin of the eukaryotic endomembrane system, however, incorporates the observations available for prokaryotic OMVs. Here we close that gap with an evolutionary inference that accounts for the origin of the eukaryotic endomembrane system in a novel and natural manner.

Prokaryotic Vesicle Secretion

As Deatherage and Cookson [15] write, it has long been known, but underappreciated, that bacteria and archaea generate OMVs. Both Gram-negative [16] and Gram-positive [17] bacteria secrete OMVs that stem from their outer membrane (Figure 2). In addition, some bacteria form nanowires, long tube-like protrusions of the outer membrane [18]. Bacterial OMV cargo ranges from outer membrane proteins to the content of the periplasmic space, which can be specifically apportioned for inclusion into OMVs [19]. OMVs are also clinically important as they can include key toxins associated with bacterial virulence and toxicity [20,21]. The rate of OMV secretion and the nature of their content can vary according to nutrient availability, stress, host–pathogen interactions, and exposure to antibiotics such as gentamicin [9,20]. The mechanistic details behind OMV release are still poorly understood, but in Gram-negative bacteria the release of OMVs is thought to result from the interplay of peptidoglycan, surface proteins, and the LPS complexes themselves [10,15,16,21,22].

Archaea also secrete OMVs [15,23], which contain proteins of the S-layer, components of the outer membrane [24], and in some cases also toxins [25]. The release of archaeal OMVs involves the Cdv (cell division) proteins A, B, and C [24,26], which are homologous to members of the eukaryotic **ESCRT** III protein family involved in membrane vesicle scission [27]. In addition to their role in OMV secretion, archaeal Cdv proteins are involved in cell division (Figure 2). While bacteria require FtsZ for cell division, many archaea lack FtsZ, with the formation of the division ring and the final scission of the daughter cells being mediated by Cdv proteins [26]. Similar to their role in cell division [26,27], Cdv proteins could aid in the tethering and scission of the membraneous neck that leads to the release of the nascent OMV from the archaeal plasma

Glossary

Archaeal lipids: membrane lipids composed of isoprenoid hydrocarbon side chains linked via an ether bond to glycerol-1-phosphate.
Autophagosomes: double-membrane-bound compartments involved in the degradation of intracellular proteins and organelles through autophagy. Outer membrane fuses with the lysosome to form the autolysosome.
Bacterial lipids: membrane lipids composed of a glycerol-3-phosphate linked to fatty acid side chains via an ester linkage.
Coatomer: class of proteins involved in vesicle coat formation. Many share a similar domain architecture uniting a β-propeller and an α-solenoid domain.
Endomembrane system: elaborate membrane system unique to eukaryotes; it includes the nucleus, the endoplasmic reticulum, the Golgi apparatus, the lysosome, the peroxisome, autophagosomes, and the myriad vesicle-trafficking processes that interconnect them with each other and the plasma membrane.
Endosomal sorting complex required for transport (ESCRT): multicomponent machinery subdivided into ESCRT-0, I, II, III; it facilitates membrane vesicle budding 'away' from the cytoplasm.
Flagellar pore complex (FPC): also known as the ciliary pore complex, a structure composed of many proteins that share a high degree of homology with the nuclear pore complex (NPC) and regulates transport into the flagellum.
Glyoxysome: specialized type of peroxisome found in plants and some fungi.
Golgi apparatus: highly dynamic structure of ordered stacks that act as a sorting station for vesicular trafficking from ER to the plasma membrane and other compartments.
Lokiarchaea: recently discovered archaeal phylum that monophyletically branches with eukaryotes.
Lysosome: acidified compartment and final destination for the degradation of proteins and particles coming from multivesicular bodies (MVBs).
Mitochondria-derived vesicles (MDVs): vesicles that originate from the mitochondria and fuse with