

Coatomer in the universe of cellular complexity

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ABSTRACT Eukaryotic cells possess considerable internal complexity, differentiating them from prokaryotes. Eukaryogenesis, an evolutionary transitional period culminating in the last eukaryotic common ancestor (LECA), marked the origin of the eukaryotic endomembrane system. LECA is reconstructed as possessing intracellular complexity akin to modern eukaryotes. Construction of endomembrane compartments involved three key gene families: coatomer, BAR-domain proteins, and ESCRT. Each has a distinct evolutionary origin, but of these coatomer and BAR proteins are eukaryote specific, while ESCRT has more ancient origins. We discuss the structural motifs defining these three membrane-coating complexes and suggest that compared with BAR and ESCRT, the coatomer architecture had a unique ability to be readily and considerably modified, unlocking functional diversity and enabling the development of the eukaryotic cell.

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THE EUKARYOTIC BAUPLAN AND THE ROLE OF COATING COMPLEXES

A hallmark of eukaryotic cells is elaborate internal membrane-bound compartments, collectively termed organelles, that facilitate segregation of specific biochemical functions (Rout and Field, 2017). While many prokaryotes do have membranous organelles, these are considerably less diverse, limited to one or a handful in each species. Although the genetic origins of the eukaryotic endomembrane system descended from prokaryotes, eukaryotes share few structures and mechanisms with prokaryotic organelles (Figure 1A) (Grant *et al.*, 2018). Moreover, it is likely that the last common ancestor of all eukaryotes (LECA) possessed an intracellular mem-

branous organelle cohort essentially as elaborate or even exceeding those possessed by their modern descendants (Rout and Field, 2017)

The basic functions of protein families involved in organellogenesis are an ability to bend and mold membranes, and at least three perform this function in eukaryotes, all of which were present in the LECA. The first, BAR-domain proteins are alpha-helical bundles and polymerize to form scaffolds of varying curvatures. The second, the ESCRT complex, operates by polymerization of alpha-helical subunits into ring or helical structures. Finally, the coatomer system predominantly comprises arrangements of extended alpha-helical sole-noids flanked or associated with beta-propellers. Despite the ability of BAR, ESCRT, and coatomer to fulfill similar mechanistic roles, their evolutionary origins, subsequent evolutionary trajectories, and the modern functions of each are very distinct (Figure 1B) (Field *et al.*, 2011; Rout and Field, 2017).

Given this, there is potential redundancy among BAR, ESCRT, and coatomer complexes in terms of their ability to deform membranes. Hence we ask, was there competition among these membrane-coating complexes to obtain the newly emerging functionalities required in the cell as it elaborated and diversified its internal membrane organization? Alternatively, was there cooperativity among them in generating membrane-bounded organelles, or even mutual indifference, as their unique architectures propelled their evolution along very separate routes? We also consider the structural plasticity within BAR, ESCRT and coatomer protein families and specifically the architecture of proteins within each family and how these subunits assemble to form a membrane coat. From this, we ask if certain inherent properties of the

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Abbreviations used: BAR, Bin, Amphiphysin and Rvs; CEP55, centrosomal protein of 55 kDa; CHMP, charged multivesicular body protein; ESCRT, endosomal sorting complex required for transport; F-BAR, FCH-BAR, or EFC for extended FCH homology preceding the BAR; FECA, first eukaryotic common ancestor; GATOR2, Seh1-associated GAP activity to TOR 2; HRS/STAM, hepatocyte growth factor-regulated tyrosine kinase substrate and signal transducing adaptor molecule; I-BAR, inverse BAR; LEACA, last eukaryotic archaea common ancestor; LECA, last eukaryotic common ancestor; LEM2, LAP2, emerin, MAN1 domain protein 2; LUCA, last universal common ancestor; mTORC1, mammalian target of rapamycin complex 1; N-BAR, N-terminal amphipathic helix preceding the BAR; NPC, nuclear pore complex; PspA, phage shock protein A; SEACAT, SEA subcomplex activating TORC1; Snf7, sucrose nonfermenting protein 7; Vipp1, vesicle-inducing protein in plastids1.

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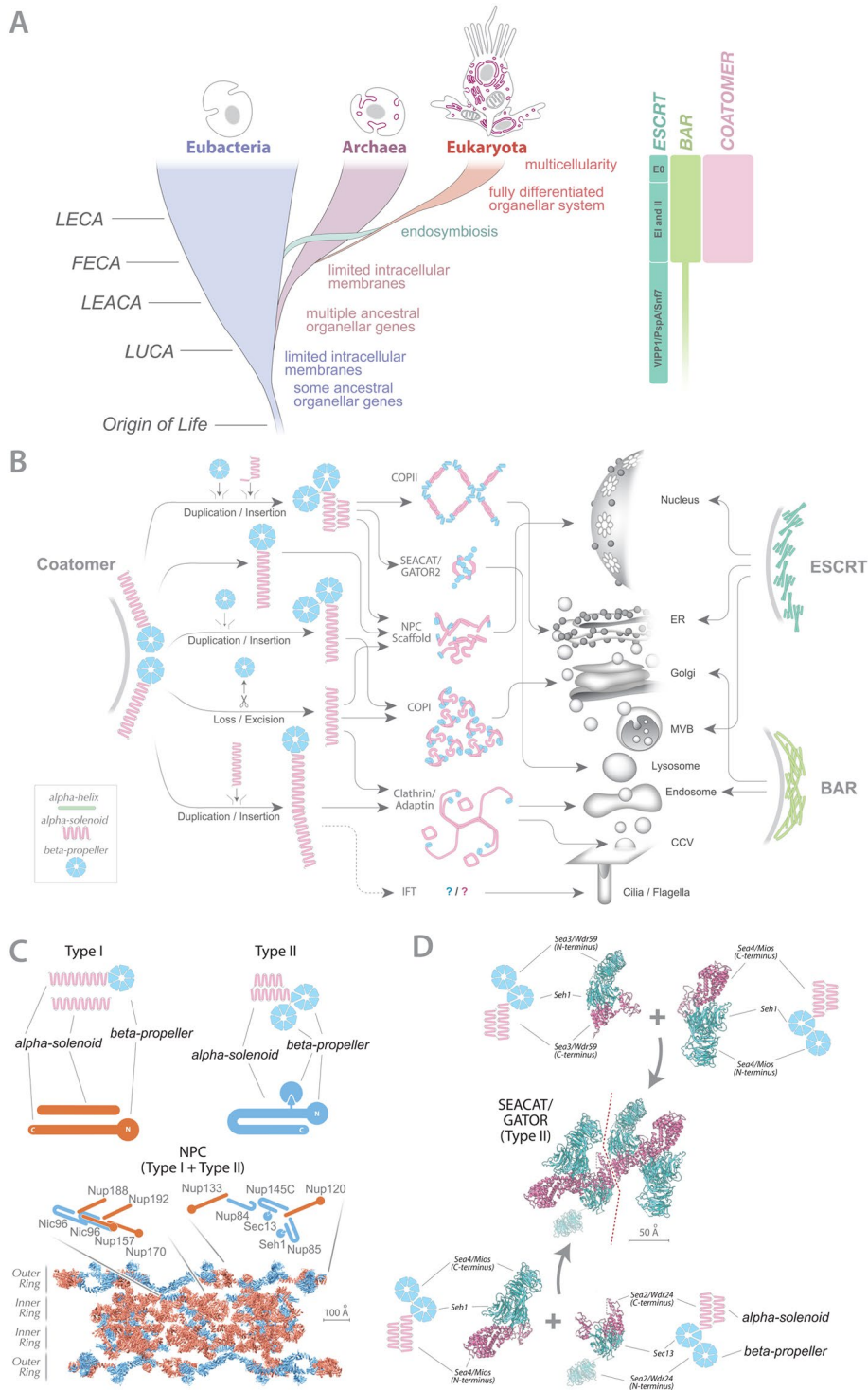


FIGURE 1: Coats, compartments, and eukaryotic origins. (A) Left: Eukaryotes arose as a branch of the Archaea. The three major lineages of life are shown together with conceptualized diagrams of cell structure; for Eukaryota, we show a choanocyte and amoebocyte from a sponge, among the earliest forms of multicellularity. Major evolutionary events are also shown together with probable timings for origins of membrane coats. LECA, last eukaryotic common ancestor; FECA, first eukaryotic common ancestor; LEACA, last eukaryotic archaeal common ancestor; LUCA, last universal common ancestor. (A) Right: approximate relative timings of origins of the coating complexes discussed here. See text for other details. (B) Structural characteristics, evolutionary paths, and intracellular locations for major functions for coatomers, BARs, and ESCRTs. Schematics for cellular compartments are at center right in gray. Arrows indicate approximate locations where individual complexes operate in the cell. Data are a composite from multiple cells/lineages, and not all locations for these complexes are shown for

underlying coatomer architecture, in contrast with those of the BAR and ESCRT complexes, were the driving factors behind expansion of coatomer into a wide variety of different coating architectures.

THE EVOLUTIONARY ORIGINS OF COATING COMPLEXES

The ESCRT complex consists of several sub-complexes known as E0, I, II, and III in metazoa, with an EIII-associated complex that incorporates the Vps4 ATPase, a regulator for ESCRT assembly. The majority of EIII and EIII-associated subunits likely arose by paralogous expansion and, except for E0, the entire system was present in the LECA (Leung et al., 2008). In metazoan ESCRT supports endosomal trafficking, protein turnover, cytokinesis, repair of the nuclear envelope, and plasma membrane fissures among many other roles (Figure 1B). ESCRT-mediated membrane bending involves a core set of Snf7-domain (CHMP in metazoan) proteins, but recruitment to individual subcellular sites in metazoa requires specific receptors, for example, LEM2 for nuclear events, HRS/STAM for late endosomes, and CEP55 during cytokinesis (Vietri et al., 2020). Importantly, Snf7-domain/CHMP proteins are structurally conserved, albeit that distinct CHMP paralogues can bend membrane with specific topology; for example, CHMP4 forms flat spirals, but CHMP1B forms positively curved spirals (McCullough et al., 2015). Thus new ESCRT roles have arisen largely by adding differential targeting modules to a conserved core and bringing essentially the same coating complex to different membranes.

Snf7-domain proteins have a clear prokaryotic origin and were likely present in the

simplicity. (C) Neofunctionalization of coatomer architectures to form the NPC. Type I (red) and type II (blue) coatomer architectures are shown, with idealized structures above (see key to B). A section of the *Saccharomyces cerevisiae* NPC structure viewed from the side is shown at the bottom, illustrating only the type I- and type II-related subunits, similarly colored red (Type I) and blue (Type II). Note the intermixing of types within the overall structure. (D) Stepwise conceptual assembly of SEACAT/GATOR2 from paralogous and identical duplications of a basic type II coatomer architecture. Schematic structures of the progenitor coatomer units are shown (see key to B) next to ribbon representations of subunits, with beta-propellers in cyan and alpha-solenoids in magenta. The beta propeller of Wrd59 is shown as translucent as its structure has not yet been solved.

earliest cells (Figure 1A). Vipp1/PspA, found in chloroplasts and bacteria, respectively, form rings and rods *in vitro* (Junglas *et al.*, 2021; Liu *et al.*, 2021) and possess an alpha-helical structure remarkably homologous to the eukaryotic Snf7 domain. Further, Archaeal Snf7 homologues function in cytokinesis (Samson *et al.*, 2011) and, while representation of ESCRT homologues across the Archaea is patchy (Caspi and Dekker, 2018), a role in cell division persists into eukaryotes including in metazoa (McCullough *et al.*, 2018). Hence the core membrane-deforming components of ESCRT have a very ancient origin and remained essentially structurally invariant for billions of years.

BAR-domain proteins can be categorized into one of three subfamilies: classical (or N-) BAR or the F- and I-BAR domain subfamilies. Significantly, N- and F-BAR polymers subtend a positive curvature, while I-BAR polymers are flat or negatively curved (Carman and Dominguez, 2018; Simunovic *et al.*, 2019). BAR-domain proteins participate in a wide variety of membrane events, including collaboration in clathrin-mediated transport, organelle shaping, and as components of the retromer complex (Figure 1B) (Carman and Dominguez, 2018; Simunovic *et al.*, 2019). While, like ESCRT, the core-coating structure remains similar across the family (Figure 1B), most BAR proteins also possess additional domains, conferring specificity and additional functionality. At least some BAR-domain proteins were considerable LECA components and originated at that time, although with evidence for lineage-specific expansion later in eukaryotic evolution (Figure 1A) (Koumandou *et al.*, 2011). The presence of BAR-domain proteins in bacteria is sparse and is possibly a lateral gene transfer from a eukaryotic donor (Phillips *et al.*, 2021). Significantly, neither the ESCRT nor the BAR protein families appear malleable in terms of architecture, with comparatively subtle variation among paralogues facilitating altered membrane curvature but with polymerized assemblies retaining highly similar structures and are frequently homopolymers (Carman and Dominguez, 2018; McCullough *et al.*, 2018).

The final system we consider is the coatomer family. The major features of this family are proteins with beta-propeller domains at the N-terminus and alpha-solenoid domains at the C-terminus as well as components comprised of either alpha-solenoids or beta-propellers alone; both domains are formed from highly repetitive motifs and can form long and flexible subunits. In contrast with ESCRT or BAR proteins, the coatomer subunit architecture displays notable structural plasticity, allowing for highly diverse architectures (Figure 1, B–D) (Bethune and Wieland, 2018; Dacks and Robinson, 2017; Rout and Field, 2017). The origins of the many different coatomer complexes from a progenitor “protocoatomer” complex have been described by us elsewhere (Devos *et al.*, 2004; Field and Rout, 2019; Rout and Field, 2017).

Coatomer architectures have been evolutionarily molded from this original protocoatomer into two major classes; type I, typified by clathrin-coated vesicles and COPI transport vesicles, and type II, typified by COPII transport vesicles. Coatomers also form assemblies with other roles, including intraflagellar transport complexes, nuclear pore complexes (NPCs) and the SEACAT (Seh1-associated) complex involved in nutrient sensing (Figure 1B) (Field *et al.*, 2011; Rout and Field, 2017; van Dam *et al.*, 2013). Indeed, coatomers were clearly instrumental in the formation and maintenance of the majority of defining eukaryotic organelles, including the endoplasmic reticulum, Golgi complex, lysosomes, endosomes, cilia, and the nuclear envelope. The coatomer paralogues that populate most of these organelles were established prior to the LECA (Figure 1A) (Rout and Field, 2017). There is currently no

evidence for coatomer being present in the Archaea, suggesting an origin initiated post the first eukaryotic common ancestor (FECA; Figure 1A) (Field and Rout, 2019; Rout and Field, 2017).

ADAPTABILITY AND CONSTRAINTS IN COATING COMPLEX STRUCTURE

Functional expansions can be mediated by gene duplications and subsequent sequence divergence among the resulting paralogues (Kuzmin *et al.*, 2021). If the original paralogue is retained, we have suggested that this represents a mechanism to evolve new membrane coats and hence compartments (Dacks and Field, 2007). However, there is significant constraint, as any heteropolymer containing both old and new paralogues must still assemble a functional coat, and structurally incompatible paralogues are likely to be a selective disadvantage. For BAR and ESCRT membrane-deforming subunits, which are both based on reflexed and heavily intertwined alpha-helices (Figure 1B) (Carman and Dominguez, 2018; Simunovic *et al.*, 2019), this most likely provides considerable restraint to novelty and consistent with the high conservation of Snf7/CHMP and BAR-domain protein and polymer structures (Figure 1B).

The coatomer complexes, stand in sharp contrast with such assemblies in terms of their constituent folds. Coatomer beta-propellers generally limit themselves to seven repeated blades in a circle and associate with other subunits either by constituting the N-terminus to an alpha-solenoid C-terminus, or indirectly via donation of one of their blades to an alpha-solenoid protein but again near the latter’s N-terminus (e.g., Valenstein *et al.*, 2022) (Figure 1B). The alpha-solenoids are a simple linear repetition of an alpha-helical zig-zag and, by contrast, demonstrate great variability in architecture, but generally through indels, kinks, or hairpin turns along the length of the alpha-solenoid rod (Figure 1B). These relatively repetitive and linear coatomer structures form assembly contacts largely limited to the ends of each subunit, which means that deletions or insertions within their repetitive sections—and particularly the alpha-solenoids—are likely better tolerated in coassembly with the original version. As a result, a hybrid coatomer coat would be more likely to retain function and not act as a dominant negative compared with BAR and ESCRT (Dacks and Robinson, 2017; Field and Rout, 2019). This gives the coatomer family a clear path to neofunctionalization and is supported by the enormous morphological diversity within members of the family (Figure 1B) (Traub, 2009; Sochacki *et al.*, 2017; Bethune and Wieland, 2018).

Membrane-bending ESCRT proteins arose in bacteria and therefore suffered for a considerable time or no competition from either BAR or coatomer complexes, neither of which evolved for over a billion years prior to eukaryogenesis. We suggest this is compelling evidence that, despite participation in an increasing number of functions, ESCRT was unable to fulfill the roles required to diversify intracellular architecture to the level of modern eukaryotes. Additionally, the limited roles of BAR-domain proteins since their origin prior to the LECA suggest a similar constraint, albeit with considerable expansions in some modern lineages where a role in facilitating post-LECA innovations is recognized (Suetsugu *et al.*, 2010).

EXAMPLES OF COATOMER NEOFUNCTIONALIZATION

How adaptable have coatomer complexes proven? We consider two examples, the NPC and the SEACAT/GATOR2 complex. Detailed structural information has recently been obtained for both structures, allowing us to examine whether and how their evolution utilized the considerable structural flexibility of the basic coatomer architecture (Kim *et al.*, 2018; Akey *et al.*, 2022; Bley *et al.*, 2022;

Fontana *et al.*, 2022; Mosalaganti *et al.*, 2022; Petrovic *et al.*, 2022; Valenstein *et al.*, 2022; Zhu *et al.*, 2022).

The NPC is a hub for protein and RNA transport across the nuclear envelope, an organizer for RNA processing and the nuclear interior (Devos *et al.*, 2004; Hayama *et al.*, 2017; D'Angelo, 2018; Holzer and Antonin, 2018; Lin and Hoelz, 2019; De Magistris, 2021; Fernandez-Martinez and Rout, 2021; Paci *et al.*, 2021). To meet these many demands, the NPC has some of the more extreme neofunctionalizations of coatomer architecture necessitating multiple duplications, alterations, and amalgamations in their constituent coatomer-related components. It is far from the original role of a membrane-deforming complex (Figure 1C).

Well over half of the mass of the NPC is composed of coatomer proteins (Devos *et al.*, 2006; Hayama *et al.*, 2017; Rout and Field, 2017; Beck *et al.*, 2018; Kim *et al.*, 2018; Field and Rout, 2019; Fernandez-Martinez and Rout, 2021). The NPC formed through an amalgamation of both type I and type II coating complexes; this complex formed early in the evolution of the NPC (Field and Rout, 2019), and subunits subsequently duplicated and diverged several times to form the inner and outer ring complexes of the NPC scaffold, resulting in both type I- and type II-derived coatomer proteins intertwined throughout the scaffold, a major elaboration not seen in other coatomer complexes to date (Figure 1C) (Field and Rout, 2019).

This flexible approach to construction extends to a high degree of heterogeneity in architecture, both within and between species, much of this generated by the addition or subtraction of outer rings on the nuclear and cytoplasmic NPC faces (Kim *et al.*, 2018; Akey *et al.*, 2022; Bley *et al.*, 2022; Fontana *et al.*, 2022; Makarov *et al.*, 2021; Mosalaganti *et al.*, 2018 #1180; Mosalaganti *et al.*, 2022; Petrovic *et al.*, 2022; von Appen *et al.*, 2015; Zhu *et al.*, 2022; Zimmerli *et al.*, 2021). Thus while their proto-coatomer ancestors were largely restricted to forming vesicle coat complexes, NPCs have been extensively modified and adapted for differential roles between organisms.

The SEACAT complex is a subcomplex of the larger SEA complex and an excellent exemplar of the proto-coatomer hypothesis in general (Devos *et al.*, 2004) and more specifically proposals here concerning extreme adaptability. The SEA complex was first identified in yeast and then in mammalian cells and as likely present in the LECA and is a major regulator of the stress response regulator mTORC1, conveying the status of arginine and leucine levels (Dokudovskaya *et al.*, 2011; Bar-Peled *et al.*, 2013; Loissell-Baltazar and Dokudovskaya, 2021; Valenstein *et al.*, 2022). We proposed that SEACAT was evolutionarily related to coatomers despite being a regulator and not a membrane-coating complex, as SEACAT subunits have predicted structural homology to coatomer, and the complex incorporates bona fide coatomer subunits Sec13 and Seh1, taken from COPII/NPC and the NPC, respectively (Dokudovskaya *et al.*, 2011; Field and Rout, 2019). Indeed a recently solved mammalian SEACAT complex structure (Valenstein *et al.*, 2022) elegantly confirms this proposal, revealing that almost the entire scaffold comprises iterations of type II coatomer subunits. Furthermore, as with the NPC, it is possible to reconstruct how the complex may have arisen from a simple type II coatomer that duplicated, diverged, and multimerized into a full octameric complex as seen today (Figure 1D). These examples of coatomer adaptability compared with BAR and ESCRT family proteins underscore a potential particular to coatomer complexes for wide plasticity in architecture and function.

IMPLICATIONS

To conclude, we suggest that ESCRT, despite a presence in the earliest cells, was unable to unlock the functions required for eukaryo-

genesis, and that this block was likely due to structural inflexibility. BAR-domain proteins arose at around the same time as coatomers but are less structurally diverse than coatomer. Hence neither ESCRT nor BAR-domains competed with coatomer for the functions the latter took on, as they were simply unable to fulfill these roles. Significantly, as expanded intracellular complexity arose, driven by the expansion and diversification of the coatomer family, new functional opportunities were created that *could* be populated by adaptations of the BAR and ESCRT families. For example, the BAR-derived retromer complex, associated with the Golgi complex, could only have arisen after the COPI and COPII coatomer complexes formed the Golgi apparatus, while roles in nuclear envelope repair and NPC surveillance undertaken by ESCRT required prior evolution of the nuclear envelope and NPC. Thus a process of cooperation to further elaborate endomembrane functions operated to generate the full complexity of the LECA and modern eukaryotes, but it appears that coatomer alone unlocked the original and full eukaryotic blueprint.

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