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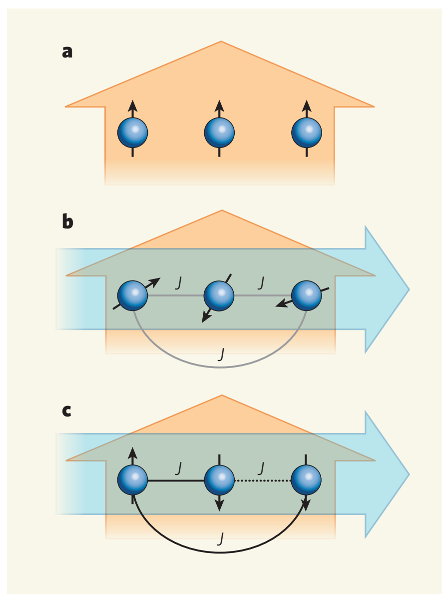

Figure 2 | **Trapped-ion quantum emulator[5].** Kim and colleagues[1] emulate a frustrated three-spin magnetic system (Fig. 1) by using three ytterbium atomic ions in an electromagnetic trap. The internal state of each ion (blue spheres) acts as a spin. **a**, All ions are prepared in a known, non-interacting ground state — here, all three ions are in the spin-up state. This is the ground state of the system in the presence of a magnetic field, which is emulated by irradiating the ions with laser light (orange arrow). **b**, An interaction (J) between the ions is switched on by slowly ramping up the intensity of additional laser light (blue arrow). This brings the system into a new interacting ground state. **c**, The new ground state is characterized by identifying the state of the individual ions. As predicted for a frustrated three-spin magnetic network, the spin of one ion is found to align opposite to those of the other two.

emulator as well as a solid understanding of its individual building blocks. This is exactly where the strength of a system of trapped ions lies. The precise behaviour of single ions and atoms is known, and, as several experiments investigating quantum-information processing have shown, a large class of quantum states can be engineered[3,4]. These considerations mean that trapped atomic ions[1,5,6] are a very attractive alternative to quantum emulators based on atoms in optical lattices[7,8]. Thus, in 2004, Porras and Cirac worked out[5] the blueprints of a trapped-ion quantum emulator (Fig. 2). And some four years later, Friedenauer *et al.* built[6] the first prototype based on two magnesium ions, and simulated a tiny quantum magnet composed of two spins.

In their study, Kim *et al.*[1] have taken a major step towards the creation of reasonably sized quantum emulators. To couple the three ionic spins to one another, they periodically stimulate the ions with laser light of appropriate frequency. Although this trick has a long-standing tradition in quantum-information-processing experiments[3,4,9], here the ionic motion used to mediate the coupling is in a direction perpendicular — not parallel — to the axis of the string formed by the ions. This allows the authors to obtain arbitrary control over the two-body interaction between all three spins (Fig. 1). In this way, they gain access to various ferromagnetic (spins aligned) and antiferromagnetic (spins opposing) ordered states, or quantum phases. By choosing an antiferromagnetic interaction, the authors prove that the ground state of the frustrated three-spin quantum network indeed contains entanglement as expected. But more importantly, the approach lends itself to a 'scalable' architecture — that is, more spins can be added to the system without running into known conceptual difficulties. Kim and colleagues' experiments suggest that quantum emulators based on trapped ions can be extended to tens of ions, possibly in the next couple of years. Such devices could emulate a large class of many-body quantum systems that are otherwise inaccessible, and so allow many interesting questions in quantum many-body physics to be addressed.

Only the future can tell whether quantum-emulation devices will eventually help us to discover novel quantum phenomena, identify new quantum phases or just design interesting quantum materials. Many roadblocks, including insufficient quantum control and quantum-state 'decoherence', will be encountered during this long journey. But none of them seems insurmountable. ■

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CELL BIOLOGY

How to don a coat

Linton M. Traub and Beverly Wendland

Cargo-carrying vesicles can assemble from hundreds of locations on the cell membrane, but how these sites are selected has been unclear. A small family of membrane-sculpting proteins may select the perfect location.

Proteins and lipids are shuttled between membrane-bounded cellular compartments by vesicular carriers. Each time the cargo is moved from one cellular location to another, these spherical structures are fabricated anew, typically from the membrane where the journey begins. But what is it that marks specific regions of the donor membrane as appropriate sites for vesicle formation? This question is particularly vexing with regard to vesicles coated with the protein clathrin that arise from the inner leaflet of the cell membrane — these structures oversee the internalization of a vast array of cell-surface proteins and extracellular molecules in a process called endocytosis. In a paper in *Science*, Henne *et al.*[1] provide a clue to how discrete clathrin-coated zones are initiated. Placement of the muniscin family of proteins[2] (FCHO1, FCHO2 and, in yeast[2–4], Syp1p) seems to demarcate cell-membrane patches for clathrin assembly.

For certain membrane-bounded intracellular organelles — the endoplasmic reticulum, the Golgi complex and endosomes — strategically positioned proteins called guanine-nucleotide exchange factors deposit regulatory GTPase molecules to prime the assembly of compositionally distinct coats. Clathrin coats assembling on the cell surface, however, are atypical: their formation is not regulated by GTPase switches. So what governs the positioning of clathrin at the cell membrane?

Clathrin-coated vesicles have three main components: clathrin, a sorting adaptor complex termed AP-2 and transmembrane cargo proteins. Early models conjectured that assembly begins when AP-2 simultaneously binds the other two components. But AP-2 does not assemble on intracellular organelles, where many of the same cargo proteins are present at high concentrations. Also, in its initial conformation, AP-2 cannot easily recognize cargo[5], indicating that another compartmental cue must restrict its assembly to the cell membrane.

This positional information comes from the lipid PtdIns(4,5)P_2, to which AP-2 binds through multiple sites. We now also know that AP-2 is a central interaction hub (Fig. 1), with more than 20 established binding partners. AP-2 therefore acts as an organizational scaffold that associates with several partners synchronously. It thus governs the formation of clathrin coats through unrelated but parallel binding events. But because coats can still form in cells with diminished AP-2 levels, other molecules must also initiate clathrin assembly.

Henne *et al.*[1] use live-cell imaging to show

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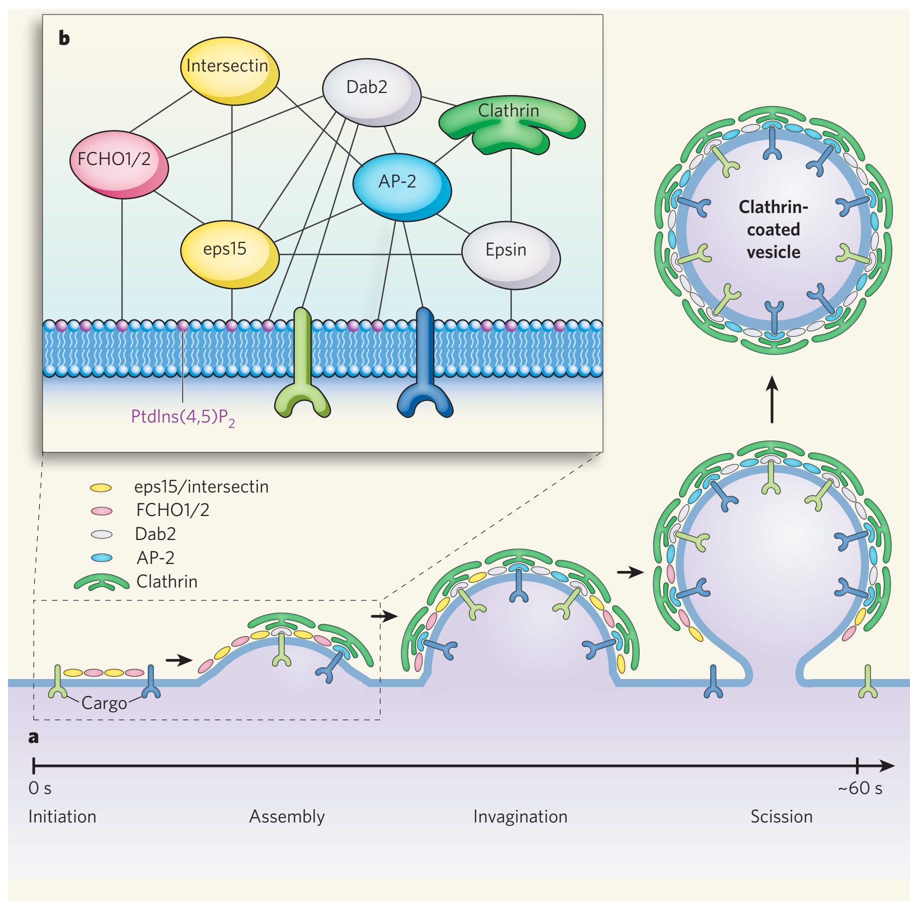

Figure 1 | Clathrin-coat assembly. **a,** Henne *et al.*[1] show that clathrin-coat formation at the cell surface begins as small assemblages of pioneer proteins called FCHO1 and FCHO2; recruitment of the endocytic proteins eps15 and intersectin probably coincide with this event. The region destined to become a bud then further expands laterally through the addition of components arriving later, such as AP-2, Dab2 and clathrin. Within a minute, it gently curves, invaginates deeply and constricts at the base. Finally, scission releases the coated vesicle. **b,** The initiation protein complex centres on core components with multiple common but weak and/or transient interactions (lines). Many of the early-arriving proteins bind to the lipid PtdIns(4,5)P_2. These proteins require AP-2 and Dab2 to link with clathrin and numerous classes of cargo.

that recruitment of the related proteins FCHO1 and FCHO2 precedes AP-2 arrival on the cell membrane and so argue that these proteins define the sites of coat assembly. That FCHO2 arrives early is concordant with findings[3,4] for its related yeast protein Syp1p.

In order to function, FCHO1 and FCHO2 require the structural EFC/F-BAR domain at their amino terminus and the μ-homology domain (μHD) at their carboxyl terminus[1,2]. The EFC domain has a crescent-shaped antiparallel dimer structure, which binds PtdIns(4,5)P_2-enriched membranes and can polymerize into rings, generating membrane tubules of various diameters[1,2]. The μHD, which is structurally similar[2] to the cargo-binding μ2 subunit of AP-2, associates directly with some of the endocytic machinery involved in clathrin-coat assembly; specifically, it interacts with the proteins eps15 (refs 2,6) and intersectin[1] in mammals and with an eps15-related protein, Ede1p, in yeast[2].

Henne *et al.* report that mutations in the EFC domain of FCHO2 that disrupt tubulation lead to static, non-functional clathrin patches in cells. What's more, SGIP1 — an FCHO1/2-related protein that lacks the EFC domain[6] — cannot substitute for FCHO1/2 despite having a μHD[1], indicating a key role for the EFC domain. Lateral oligomerization of EFC dimers into a membrane-moulding polymer is intuitively appealing, and the authors[1] assert that contouring of the bud site is vital for coat initiation and progression.

But is the crucial role of FCHO1/2 really to dimple the underlying membrane, or is it to pair with eps15 and intersectin, which in the fruitfly *Drosophila* are needed for the membrane placement of several endocytic factors[7]? In the absence of clathrin, assembly zones rich in AP-2 (and presumably FCHO1/2) are invariably flat[8]. Also, EFC domains may be auto-inhibited, requiring association with other partners to promote polymerization[9]. When eps15 and intersectin are depleted, FCHO2 diffuses over the cell surface[1] to mirror the PtdIns(4,5)P_2 distribution instead of populating small spots that designate bud sites. This indicates that binary associations with the μHD partners are required for clustering of PtdIns(4,5)P_2-bound FCHO1/2, and explains why, in addition to the EFC domain, the μHD seems necessary.

Emergent clathrin coats abort if appropriate cargo is not incorporated[10,11]. Like AP-2, FCHO1/2 may bind directly to cargo, mediating its incorporation into the incipient bud; this is indeed true for the related Syp1p protein[2]. Alternatively, muniscins could couple bud-site selection with cargo availability, as their binding sites on eps15 and intersectin are different from those for interaction with AP-2 and two other later-arriving cargo-binding factors, Dab2 and epsin. FCHO1/2 could thus organize eps15 and intersectin for optimal recruitment of AP-2, Dab2 and epsin (Fig. 1b). For example, eps15 restriction to the margins of growing patches destined to be coated with clathrin may be facilitated by FCHO1/2, which could allow AP-2 deposition and cargo capture in the centre of the patch.

Even assuming that FCHO1/2 are 'pioneer' components, proportional amounts of them would be required to operate as initiators that oligomerize and organize coated buds. For much of their work, Henne and colleagues used overexpressed protein, but the cytoplasmic concentration of native FCHO proteins (and other coat constituents) relative to AP-2 and clathrin is unknown. Also perplexing is the fact that — in a vast multi-parametric screen of more than 4,500 genes that affect endocytosis[12] — reducing the levels of FCHO1 or FCHO2 affected the unrelated process of endosomal positioning but, surprisingly, caused no major problems with internalization.

What is clear, nonetheless, is that coat construction is shaped by a cascade of transient, low-affinity protein–protein interactions with substantial promiscuity and inherent redundancy. So, with the identification of FCHO1/2 as pioneer proteins, the veil over the pressing conceptual problem of how assembly begins has been lifted further. But, like investigations into the Big Bang, it is likely that yet earlier steps remain to fully define the true genesis of clathrin-coated pits. ■

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