A journey through the exocytic pathway

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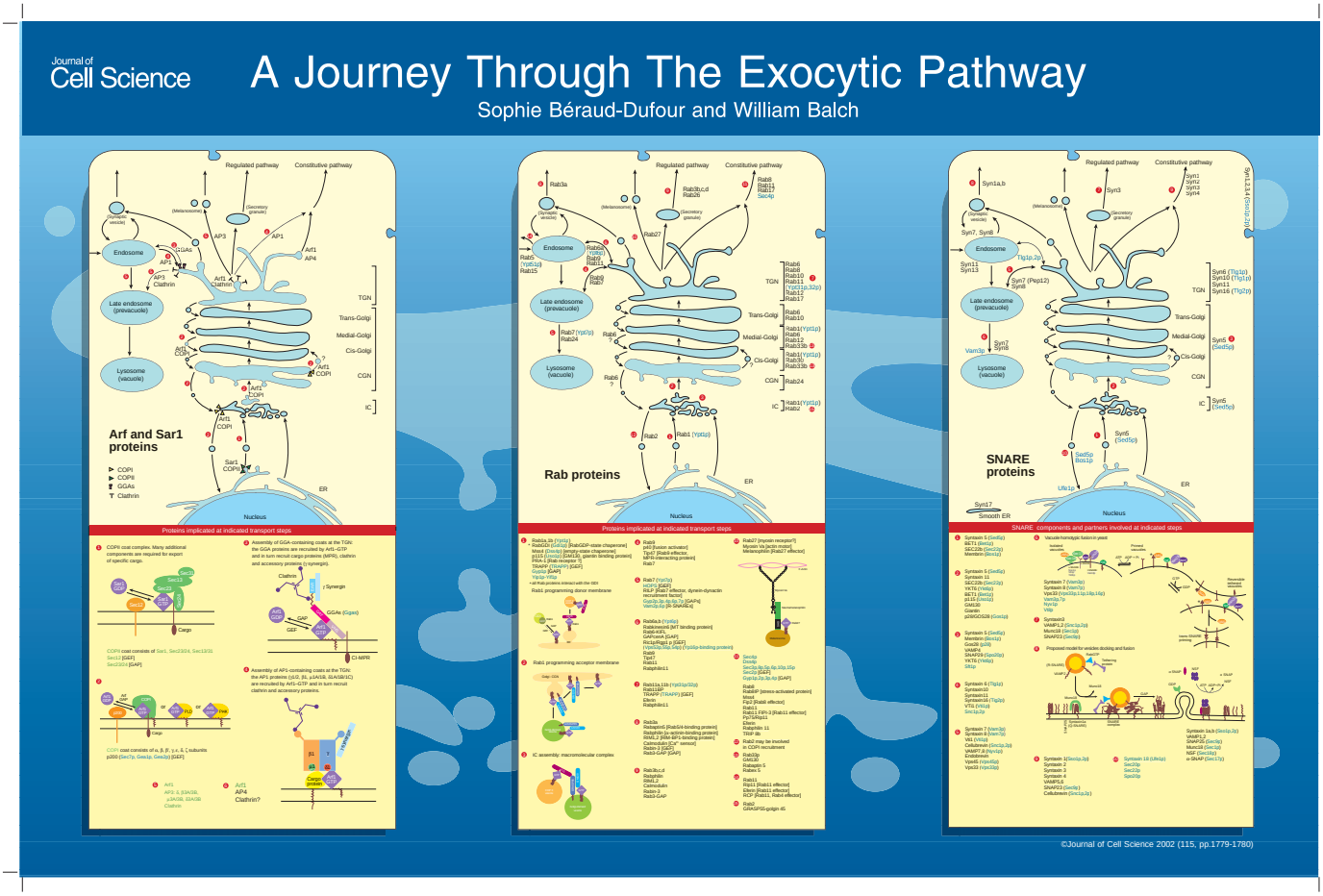
The poster is composed of three panels, which represent the three major protein families required for the journey of cargo through the exocytic pathway. These families are the ARF and Sar1 family GTPases, which are involved in vesicle formation (left panel), Rab family GTPases, which are involved in vesicle targeting (middle panel) and SNARE family proteins, which participate in vesicle fusion (right panel). The upper half of each panel illustrates the localization of these proteins to their respective transport steps and/or compartments. In both the upper and lower panels, the mammalian proteins are labeled in black and yeast proteins are labeled in blue. If the mammalian and yeast proteins utilize the same nomenclature, they are highlighted in green. The numbers within the red circles refer to additional effectors (shown in the lower half of each panel) that participate in the indicated transport step.

All eukaryotic cells contain numerous membrane-bound compartments with specialized functions and therefore unique protein compositions. The journey of proteins between these compartments starts by co-translational insertion into the endoplasmic reticulum (ER). Exit from the ER is mediated by COPII vesicles from 100-200 export sites distributed throughout the cell (left panel). COPII coat assembly is regulated by activation of the Sar1 GTPase by the ER-associated guanine nucleotide exchange factor (GEF) Sec12, which results in the formation of a microtubule-dependent scaffold that initiates cargo selection through tubular intermediates (referred to as transitional elements). Coat assembly and fission is completed by the recruitment of the Sec23/24 guanine nucleotide activating protein (GAP) complex and its regulator, the Sec13/31 complex. Upon fission from the ER, COPII-coated tubules/vesicles lose their coat in response to hydrolysis of GTP. They are subsequently believed to fuse to form the intermediate compartment (IC). Here, proteins exported from the ER can undergo two different fates, either escaped ER resident proteins and misfolded proteins are transported back to the ER via COPI-coated vesicles (left panel), or normal cargo destined for downstream compartments is retained in IC elements that are transported to the pericentriolar region, along microtubule tracks, where they fuse with other IC elements to form



(See poster insert)

the cis compartment of the Golgi apparatus.

COPI coat assembly on the IC and subsequent Golgi compartments is regulated by the ARF1 GTPase, which promotes the recruitment of the cytosolic COP complex (left panel), containing seven different subunits. ARF1 also participates in the activation of lipid kinase signaling pathways involving PLD that regulate Golgi structure and function. Cargo moves through the Golgi stack in a cis-to-trans direction by a mechanism that is likely to involve directed maturation. In this process, Golgi-resident proteins are sequentially retrieved from more terminal, mature compartments using the COPI retrieval pathway, whereas cargo is collected at the trans face. Here, cargo proteins are sorted to a variety of different destinations. Some will be transported to the plasma membrane using the constitutive pathway, others are sorted via regulated pathways to, for example, secretory granules, secretory lysosomes, such as melanosomes found in melanocytes, or synaptic vesicles that release neurotransmitter at the synapse. In addition, proteins can be transported to endosomes, late endosomes (prevacuoles in yeast) and to lysosomes (vacuoles in yeast). These pathways utilize ARF1 (or, potentially, other ARF isoforms), clathrin and adaptor proteins (AP 1-4) and GGAs to facilitate cargo segregation into distinct vesicle and tubule intermediates that direct cargo along their respective pathways.

Vesicle targeting is mediated by Rab family GTPases (middle panel). The Rab protein family now includes at least 63 isoforms in mammals and 11 in yeast. All Rab proteins are found in the cytosol in the GDP-state complexed with Rab guanine nucleotide dissociation inhibitor (GDI). The Rab-GDI complex delivers each Rab GTPase to a different membrane compartment during formation of transport intermediates, and here they are activated by Rab-specific GEFs. Activated Rabs subsequently recruit a wide variety of effectors that can mediate (1) vesicle motility through linkage to kinesin and myosin motors and/or (2) direct the tethering of transport intermediates to their target membranes. In ER-to-Golgi transport, the Rab1 GTPase found on COPII-derived tubules/vesicles recruits the tether molecule p115, which targets the intermediate to Golgi membranes containing the cognate tether complex GM130-GRASP65.

Vesicle fusion is facilitated by the activity of SNARE proteins (right panel). Fusion requires the formation of trans SNARE complexes that contain at least one R-SNARE, which is usually found on the carrier intermediate (often referred to as the vesicle-associated or v-SNARE, such as VAMP1, which is found on synaptic vesicles involved in neurotransmitter release) and several target-membrane-associated Q-SNAREs (or t-SNAREs, such as syntaxin and SNAP25 proteins, found on the presynaptic membrane). The assembly of trans SNARE complexes requires general factors such as NSF and α-SNAP that function as molecular chaperones to mediate conformational rearrangements coordinated with the activity of other regulatory proteins and signaling molecules such as Ca^{2+}. Rab GTPases are likely to play critical role in the ordered assembly of these tethering-fusion complexes. Therefore, the sequential assembly of vesicle coats that direct cargo selection (left panel) and recruitment of the targeting (middle panel) and fusion (right panel) machinery culminates in the formation of a biochemical machine that dictates the specific trafficking of proteins through the exocytic pathway.

Abbreviations used: ARF, ADP-ribosylation factor; CI-MPR, cation-independent mannose 6-phosphate receptor; COPI, coat-binding complex I; COPII, coat-binding complex II; GDI, guanine dissociation inhibitor; GEF; guanine nucleotide exchange factor; GAP, GTPase-activating protein; GGAs, Golgi-localized, γ-ear-containing ARF-binding proteins; GM130, Golgi matrix protein 130; GRASP-65, Golgi reassembly stacking protein 65; PI4K, phosphatidylinositol 4-kinase; HOPS, homotypic fusion and vacuole protein sorting; MT, microtubule; NSF, N-ethylmaleimide-sensitive factor; PLD, phospholipase D; Rab11BP, Rab11-binding protein; RCP, Rab coupling protein; RILP, Rab-interacting lysosomal protein; SNAP, soluble N-ethylmaleimide fusion protein attachment protein; v/t-SNARE, vesicular (v)- and target (t)-soluble NSF attachment protein receptors; Vam, vacuolar morphology; Vps, vacuolar protein sorting; TRAPP, transport protein particle.

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