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Review

Diverse roles for the p24 family of proteins in eukaryotic cells

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Abstract

Members of the p24 protein family form a highly conserved family of type I transmembrane proteins that are abundant components of the early secretory pathway. Topologically, the proteins have a large luminal domain and a short cytoplasmic domain that allows for targeting to both coat protein complex II and coat protein complex I vesicles, and thus these proteins cycle between the endoplasmic reticulum and Golgi compartments. Several functions have been proposed for these proteins including a role in coat protein complex I vesicle biogenesis, cargo protein selection, organization of intracellular membranes, and protein quality control. Recent studies have added to the list of potential cargo substrates for which p24 function is required for normal transport in the secretory pathway. This review focuses on recent developments in the study of p24 proteins and their requirement for secretory and membrane protein transport in eukaryotic cells.

Keywords: endoplasmic reticulum; Golgi; protein transport; p24 proteins; secretory pathway.

Introduction

There are two distinct routes of protein secretion in eukaryotes: (i) the conventional pathway, which requires the entry of the secretory cargo into the endoplasmic reticulum (ER) followed by transfer to the Golgi apparatus and then post-Golgi compartments, and (ii) the nonconventional pathway, which is independent of the ER-Golgi system (1, 2). In the conventional pathway, secretory and transmembrane proteins enter the secretory pathway via the ER. Following synthesis, folding and posttranslational modification in the ER proteins are trafficked along the secretory pathway and are delivered to their target destinations. Transport between the endomembrane compartments relies on transport vesicles. In the early secretory pathway, two distinct vesicle types exist: coat protein complex I (COPI)-coated vesicles and coat protein complex II (COPII)-coated vesicles (3, 4). COPII vesicles emerge from the ER to export newly synthesized secretory proteins toward the intermediate compartment and Golgi (5). COPI vesicles are involved in retrograde transport from the intermediate compartment and the *cis*-Golgi complex, and possibly in anterograde transport within the Golgi stack (4).

In the conventional protein secretion pathway, membrane and soluble secretory cargo are packaged into COPII vesicles at ER exit sites (5). Although some very abundant cargo proteins may access COPII vesicles at their prevailing concentration in the ER (so-called bulk flow), it is widely believed that for the majority of cargo proteins this step involves a mechanism by which cargo proteins are sorted into COPII vesicles either by interaction with components of the COPII coat machinery or by dedicated cargo receptors, which, in turn, are incorporated into COPII vesicles (6). Several protein families have been demonstrated to be involved in cargo protein selection and transport in the secretory pathway including the lectin endoplasmic reticulum-Golgi intermediate compartment – 53 (ERGIC53) and related proteins and the p24 protein family (6).

The approximately 24-kDa type I transmembrane p24 proteins comprise a relatively large family that plays vital and potentially diverse roles in protein transport in the secretory pathway. Detailed reviews describing p24 family members, their biochemical properties, and proposed functions have appeared recently (7, 8). Here, we aim to briefly introduce the p24 protein family members and their biochemical characteristics and highlight recent studies on the function of p24 protein family members in the secretory pathway in eukaryotic cells.

p24 protein family in eukaryotic cells

Members of the p24 protein family have been identified in yeast, plants, and metazoans including humans (9–11). On the basis of sequence homology, p24 proteins are grouped into four subfamilies: α, β, γ, and δ (9, 11). p24 proteins are highly conserved within a subfamily but not between subfamilies (8), and the number in each subfamily varies among species (Table 1). The yeast p24 family consists of 8 members (12–14), while the mammalian p24 family consists of 10 members (11, 15–19). Phylogenetic analysis of p24 proteins in vertebrates showed that the p24α and p24δ subfamilies

Table 1 Nomenclature of vertebrate, *Drosophila*, plant, and yeast p24 proteins.

Subfamily	Vertebrates			*Drosophila*	Plant	Yeast
	Systematic name	Systematic database name	Additional names			
α	p24α1	TMED11	gp25L	Eclair		Erp1p
	p24α2	TMED9	p25, GMP25, gp25L2, p24d, p24D			Erp5p
	p24α3	TMED4	GMP25iso			Erp6p
β	p24β1	TMED2	p24, p24a	CHOp24, CG9308	p24β1, p24β2	Emp24p
γ	p24γ1	TMED1	tp24, T1/ST2 (receptor-binding protein)	p24-1		Erp2p
	p24γ2	TMED5	p28, T1/ST2 iso	CG31787		Erp3p
	p24γ3	TMED7	(g)p27	Opm		Erp4p
	p24γ4	TMED3	p26, p24b	Logjam		
	p24γ5	TMED6				
δ	p24δ1	TMED10	p23, tmp21(-I), p24c	Baiser	p24δ1a, p24δ1b, p24δ1c (Atp24), p24δ1d	Erv25p
	p24δ2		p23iso		p24δ2a, p24δ2b, p24δ2c, p24δ2d, p24δ2e	

Adapted from (8).
opm, opossum; TMED, (Transmembrane emp24 domain-containing protein).

have a common origin, as do the p24β and p24γ subfamilies (11). The p24α and p24γ subfamilies have expanded in vertebrates, whereas the p24β and p24δ subfamilies comprise a single member. It has been speculated that this possibly might lead to a certain degree of functional redundancy within the two branches, which eliminated the need to expand both subfamilies (8). However, it has recently been shown in vertebrates that members of different p24 subfamilies and members of the same p24 subfamily may have nonredundant roles in secretory cargo biosynthesis (20), which is in contrast to the situation in yeast (13).

Plants, in contrast to animals and yeast cells, have members of only p24β and p24δ subfamilies (9, 11). There are 11 p24 proteins in *Arabidopsis* that are part of these two subfamilies (21). Some recent studies have begun to characterize the localization and interaction of these proteins, which appear to have differences in steady-state localization in the early secretory pathway (21, 22).

p24 protein structure, localization, and tissue expression

Domain structure and oligomerization

The p24 proteins have a similar domain architecture: a single transmembrane domain near the C terminus; an N-terminal luminal Golgi dynamics domain, which contains a putative disulfide bond (23); a coiled-coil domain that is involved in intermolecular interaction with other p24 proteins (24, 25), and a short C-terminal tail of approximately 13–20 amino acids at the cytosolic side (11, 15) (Figure 1). The cytosolic C-terminal tail of most p24 proteins contains dilysine (KKXX) (or dibasic) and diaromatic (FF) motifs, which can interact with COPI and COPII coat proteins, respectively (8, 15, 26, 27). Biochemical interaction studies have shown that the diaromatic motif is required for binding to the Sec23/24 component of the COPII coat (15, 27), while the dilysine motif of p24 proteins allows for binding to the γ-COP component of the COPI coat (26, 28). One or both of these motifs are also present on other sorting receptors in the early secretory pathway, including ERGIC53 a protein that also cycles between the ER and Golgi and is involved in the ER export of various secreted glycoproteins (6).

The p24 proteins exist in complexes with each other and likely interact via their luminal coiled-coil domains (24), although the cytosolic tail regions also possess oligimerization properties (8). Studies in yeast suggest that p24 complexes form heterotetramers that contain one protein of each subfamily (13). However, studies in mammals suggested that p24 proteins can also form various dimers (25). Individual members exist as dimers and monomers, and the ratio between these two forms depends on both the organelle investigated and the p24 protein. Unequal quantities have been found, with p23 (p24δ1) and p27 (p24γ4) having different concentration gradients in the early secretory pathway, ruling out a simple 1:1 stoichiometry (25). However, most p24 proteins form hetero-oligomers, essential for their correct localization and

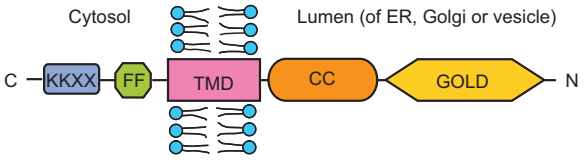

Figure 1 Schematic of the general domain organization of p24 proteins.
The structure of p24 proteins includes a short cytoplasmic tail, a transmembrane-spanning domain (TMD), a putative coiled-coil region (CC), and a Golgi dynamics domain (GOLD) with a presumed disulfide bond (not shown). The short cytosolic tail region contains both diaromatic (FF)/large hydrophobic motifs principally involved in COPII coat binding and dibasic (KK) motifs involved in COPI coat binding.

stability; for example, p23 (p24δ1) and p24A (p24β1) form a hetero-oligomeric complex (29), and interaction between p24A and p23 is required for their proper localization within cells (30).

Interestingly, interactions of p24 proteins are required for their stability. For example, TMED2 (p24β1) and TMED10 (p24δ1) regulate each other's stability, and in the absence of one protein, the level of the second interacting protein is also reduced (25, 31, 32). Thus, overexpression or knockdown of a single p24 protein generally affects the expression of other p24 family members. When protein levels of a single family member are reduced or deleted, the levels of the other endogenous p24s are reduced concomitantly (12, 13, 31, 33–35). The reduction of a single member affects the protein stability of other members. For example, reduced stability of endogenous yeast Erv25p (p24δ) is observed in cells lacking EMP24 (p24β) (12). Furthermore, the expression of exogenous p24 protein has been found to destabilize endogenous family members in some cases (36, 37).

In addition to forming oligomers, a recent study has identified a specific interaction of the p24β1 protein transmembrane domain with the lipid *N*-stearoyl sphingomyelin and that this interaction is required for the dimerization of this p24 protein (38). Such an interaction was not observed with p23 (p24δ1). Thus, in addition to protein interactions, p24 proteins may interact specifically with certain lipids that are required for their function (discussed below).

Cellular localization

In general, p24 family member proteins are most abundant in the early secretory pathway. In animal cells, p24α proteins localize primarily to the ER (15, 25, 37), while members of p24β, p24δ, and p24γ proteins are present throughout the ER-Golgi interface and cycle between the ER and Golgi (15, 30, 39–42). Surprisingly, the p24δ1 protein has been shown to be localized not only to *cis*-Golgi but also to secretory granules (40). In *Arabidopsis*, although all p24δ proteins possess classic COPII and COPI binding motifs in their cytosolic C-termini, four p24δ1 proteins including p24δ1c are localized exclusively to the ER (21, 43), and all five p24δ2 proteins can be found in both ER and Golgi. Two p24β proteins reside largely in the Golgi (21). In yeast, p24 proteins are localized not only to the ER, Golgi, and COP vesicles but also to peroxisomes (44). The steady-state localization and recycling of p24 proteins in the ER-Golgi interface is dependent on (i) their interaction with COPI and COPII coats mediated by the dilysine (KKXX) and diaromatic motifs presented in the cytosolic C-terminal tail (15, 26, 27), (ii) the interaction with other p24 proteins mediated by the luminal coiled-coil domain (30, 39), and (iii) potentially interaction with Golgi matrix proteins (45).

Tissue expression and regulated expression

Several studies have examined cell and tissue expression of various p24 family member proteins. Although, in general, most p24 proteins are ubiquitously expressed, tissue-specific expression has been demonstrated for some members, as well as regulated expression of various members in some cell types under certain circumstances. In mice, all but two p24 proteins are widely expressed. Only p24α1 and p24γ5 display restricted expression patterns, with p24γ5 showing strong expression in lung, liver, kidney, small intestine, and colon and weak expression in spleen, whereas p24α1 is highly expressed in pancreas tissue (11). A recent study has shown that p24β1 is expressed in syncytiotrophoblast, cytotrophoblast, and stromal cells during placental development in mice (42). In addition, some studies have shown that members of the p24 family are abundantly expressed in secretory cell types such as exocrine and endocrine cells (35, 40, 46). At least one member of each subfamily of p24 proteins (p24δ1, p24β1, p24α2, and p24γ3) is expressed in insulin-producing pancreatic β cells (35).

In *Xenopus*, p24 expression can be cell-type specific and selectively induced (47, 48). *Drosophila* p24 transcripts are developmentally and tissue-specifically expressed (49–51). Some p24 genes have sex-specific expression patterns and tissue- and sex-limited functions; for example, loj (p24γ4) is highly expressed in adult female tissues, particularly the ovary and the central nervous system (50). It is also likely that some p24 proteins are induced as part of the unfolded protein response to ER stress, which upregulates the secretory pathway in general (52). In support of this, p24 proteins have been identified as upregulated genes in response to ER stress (53). Furthermore, a recent study has identified that p24 proteins can be induced by the *Drosophila* CrebA/Creb3-like transcription factor that can regulate many components in the secretory pathway (54). In mammalian cells, the CrebA orthologues Creb3L1 and Creb3L2 are ER-localized ER stress response sensors that are expressed in a tissue-specific manner (55–59). Thus, p24 induction in response to ER stress may be regulated by these transcription factors in certain tissues.

Overall, the expression patterns of various p24 family members suggest that some p24 proteins may have ubiquitous roles, while others may have various specialized roles depending on the cell type.

Diverse functions for p24 proteins

p24 proteins are nonessential genes in yeast as yeast cells lacking all eight members are viable (10). In the absence of p24 proteins in yeast, induction of the unfolded protein response appears to compensate for what might be expected to be the loss of essential vesicular transport events mediated by COPI vesicles (60). However, yeast cells lacking p24 proteins do have subtle phenotypes as will be discussed below. In multicellular organisms, p24 proteins are essential genes. Knockout of p24δ1/p23 in mice is lethal (31), and TMED2 (p24β1) and TMED10 (p24δ1) are both required for the normal development of mouse embryos (31, 32). Similarly, knockdown of most of the nine p24 proteins in *Drosophila melanogaster* results in complete or partial lethality (61).

Thus, in multicellular organisms, the function of these proteins is critical for survival.

Based on their structure and cellular localization, there is little doubt that p24 proteins play a role in transport in the early secretory pathway. Their ability to access both COPII and COPI vesicles indicates that they can cycle between the ER and Golgi. However, multiple p24 family members exist in many different species, and the precise function of individual members is still for the most part unclear. Furthermore, the proposed functions for p24 proteins are numerous: a role as receptors in cargo protein selection, regulation of vesicle biogenesis (e.g., as machinery for COPI vesicle budding), maintenance and supply of machinery proteins in the secretory pathway subcompartments, and quality control of transported proteins (8, 9, 14, 17, 18, 62–67). However, it is important to note that because of their central role in the exocytic pathway, one needs to be cognizant of whether the phenotypes observed when modulating p24 function are caused by a direct or indirect function of p24 proteins.

COPI vesicle formation

Several observations suggest that p24 proteins function in COPI vesicle formation and budding in mammalian cells as reviewed in Beck et al. (68), Strating et al. (7), and Strating and Martens (8). A brief summary of the major observations is presented here. In early studies, the cytoplasmic tail of p23 was shown to facilitate the *in vitro* budding of COPI vesicles from synthetic liposomes (69). In addition, p24 proteins may act as primary receptors for GDP-bound ADP ribosylation factor 1 involved in regulating COPI vesicle formation (27, 63, 70) and bind the COPI coat complex (26, 71). Binding of p24 proteins to the COPI coat is thought to facilitate oligomerization of the coat (72, 73). Furthermore, a requirement for p24 proteins in COPI vesicle formation was demonstrated by using an *in vitro* Golgi membrane budding assay, where it was shown that p24 proteins promote budding by acting as a primer to induce COPI coat polymerization onto Golgi membranes (60). p24 proteins may also regulate COPI vesicle disassembly. p24α/p24β1 has been shown to bind Arf GTPase-activating protein 1 and inhibit its activity, preventing premature uncoating and allowing cargo selection to take place (74, 75). Finally, a recent study has shown that p24 protein binding to *N*-stearoyl sphingomyelin is required for COPI-mediated retrograde Golgi-ER transport of the *Pseudomonas aeruginosa* exotoxin A (38). Combined, these studies suggest that p24 proteins have a role in COPI vesicle biogenesis. A role in COPI vesicle formation may facilitate the cargo selection function of p24 proteins, which would allow interactions in the Golgi or ER-Golgi-intermediate compartment lumen with potential cargo proteins and efficient incorporation into newly forming vesicles. Furthermore, a role in COPI vesicle formation suggests that these proteins could be important for recycling or retrieval of components required for ER-Golgi transport or in ER function.

p24 proteins are also components of COPII vesicles and can interact with Sec23 and Sec24 components of the COPII coat (12, 14, 15, 76). p24 protein function is not essential in COPII vesicle formation, as COPII vesicles can be reconstituted *in vitro* in the absence of p24 proteins (77). However, it has recently been shown that because of their abundance and asymmetric membrane topology (i.e., majority of their mass in the lumen of the forming vesicle), p24 proteins influence the biological processes that drive COPII vesicle formation *in vivo* (78). Although a direct role in COPII vesicle biogenesis is unclear, what is certain is that p24 proteins access COPII vesicles via their ability to interact with the COPII coat. This interaction allows p24 proteins to efficiently enter COPII vesicles and thus transfer any interacting proteins to such sites. Acting as cargo protein receptors is therefore one of the key direct functions for this protein family.

Cargo protein receptor

As mentioned previously, yeast lacking all p24 proteins are viable (10). However, transport of a small number of cargo proteins is reduced in particular mutant backgrounds (12–14, 18). Deletion of one or more p24 proteins in yeast impaired the anterograde transport of some secretory cargo such as Gas1p and invertase. However, transport of other proteins such as α-factor, acid phosphatase, carboxypeptidase Y, alkaline phosphatase, and Gap1p was not affected (12–14, 18, 65). Thus, p24 proteins are not absolutely required for the transport of proteins through the secretory pathway, although the efficiency of some proteins is reduced when these proteins are absent.

More recent studies have also shown that yeast glycosylphosphatidylinositol (GPI)-anchored proteins other than Gas1p also rely on p24 proteins for efficient ER export, indicating that p24 proteins are required for efficient ER export of this class of proteins (79, 80). This is supported by recent work in mammalian cells. Knockdown of p23/p24δ1 in mammalian cells caused delayed ER-to-Golgi transport of a GPI-anchored protein but not of proteins that were not anchored to GPI (33). Using small-interfering RNA-based silencing, it has been shown that ER-to-Golgi transport of the human GPI-anchored protein CD59 requires Sec24C and Sec24D isoforms and the protein complex p24-p23 (81). Finally, members of the p24 family have been found to interact with GPI-anchored proteins, supporting the notion that these proteins act as cargo receptors (33, 79, 81). As GPI-anchored proteins have no exposure to the cytosol, p24 protein interaction would allow for more efficient packaging into COPII vesicles at ER exit sites.

It remains unclear exactly how p24 proteins recognize GPI-anchored proteins, but recent studies have identified key structural features for this interaction. Prior to ER exit, GPI-anchored proteins undergo structural modifications that are required for efficient ER export of these proteins; an acyl chain linked to inositol is removed by the enzyme PGAP1 and a side-chain ethanolamine phosphate attached to the GPI anchor is removed by PGAP5 (82). These modifications are required for the sorting of GPI-anchored proteins to ER exit

sites where COPII vesicles form and for efficient binding to p24 proteins (83).

In yeast, the GPI anchor is also remodeled and modifications are also required for sorting into COPII vesicles at ER exit sites (79, 80). However, the concentration of GPI-anchored proteins at ER exit sites does not require p24 proteins (79). Thus, p24 protein function is argued to promote efficient ER exit after they are first concentrated at these sites by linking these proteins to the COPII coat. This adaptor or linker role is supported by the observation that in yeast the disruption of the p24 protein-binding site on the specialized COPII subunit Lst1p specifically impairs the efficient ER-to-Golgi transport of the p24 cargo protein Gas1p (79). GPI-anchored proteins can associate with detergent-resistant lipid domains, which may be responsible for concentration prior to recognition by the p24 proteins. Interestingly, the p24 complex-GPI-anchor system may also be used as a quality control system to retrieve GPI-anchored proteins that fail to attain the remodeled GPI anchor by efficiently retrieving them from the Golgi (79).

Another class of lipid-modified secreted glycoproteins for which p24 function has recently been identified is the Wnt glycoproteins. These secreted signaling proteins are important in controlling animal development. Two recent studies have identified p24 proteins to be important for Wnt glycoprotein secretion in *Drosophila* and in mammalian cells (84, 85). A genome-wide RNAi screen for genes required for *Drosophila* Wg (Wingless) secretion identified the p24 proteins Emp24 and Eclair, which were required for normal ER export (85). In addition, Buechling et al. found that Opossum, Emp24/CHOp24, and p24-1 all play a role in Wg secretion (84). Furthermore, RNAi knockdown of Opossum, one of the *Drosophila* p24 members, prevents the secretion of another Wnt (WntD) in cultured cells (84). Biochemical interactions of the p24 proteins (Opossum and Wg; Emp24/CHOp24 and Wg) was detected, suggesting that p24 proteins likely act as cargo receptors required to escort Wnt proteins from the ER (84, 85). Secreted Wnt proteins are known to be lipid modified, and it is possible that this modification allows for interaction with p24 proteins that are known to mediate the export of GPI-anchored proteins as mentioned above. This intriguing possibility requires experimental verification.

p24 proteins tend to be highly expressed in professional secretory cells that produce and secrete large amounts of various secretory cargo (40, 46, 48). One such cell type that has been extensively studied is the melanotrope cell from *Xenopus laevis*. These cells secrete peptides that are produced by processing of the pro-opiomelanocortin (POMC) protein such as α-melanophore stimulating hormone (α-MSH) in a regulated manner. Six p24 members are expressed in these cells. Some (p24α3, p24β1, p24γ3, and p24δ2), but not others (p24γ2, p24δ1), are induced coordinately with the *POMC* gene (48). To study the potential function of these p24 proteins, Strating et al. generated stable transgenic *Xenopus* with expression of six p24 proteins tagged with GFP and under control of the POMC promoter. Expression of p24γ2, p24γ3, and p24δ1 did not affect steady-state levels of endogenous p24 proteins while expression of p24δ2 caused reduction in endogenous p24 protein expression (37). In terms of POMC transport, expression of p24γ3 reduced secretory protein transport, while p24γ2 had no effect (7). Interestingly, however, p24γ2 caused an increase in POMC sulfation, but not glycosylation, whereas p24γ3 did not affect sulfation, but reduced glycosylation. Both POMC sulfation and glycosylation are perturbed in the p24δ2 but not in p24δ1-expressing cells (37). In summary, these results indicate that different members may have distinct roles in the biosynthesis and transport of the POMC secretory protein. Also interesting is the fact that members from the same family appear to have distinct roles.

Another secretory cell with abundant expression of multiple p24 family members is the insulin-secreting pancreatic β cell (35). Knockdown of p24δ1 in insulinoma cell lines, which also resulted in the concomitant knockdown of other family members, impaired glucose-stimulated insulin secretion, decreased total cellular insulin content, and reduced proinsulin biosynthesis. Thus, p24δ1 and possibly other p24 family proteins are required for normal insulin biosynthesis and subsequent secretion in pancreatic β cells (35). However, whether p24 proteins act as bona fide cargo receptors for proinsulin is unclear as it was not established whether proinsulin produced in the ER can interact with one or more p24 proteins.

In addition to the examples described above, various other cargo protein functions have been ascribed to the p24 proteins. p24a/p24β1 has been found to regulate the trafficking of the G-protein-coupled receptor protease-activated receptor-2 (86). p24A (p24β1) and p23 (p24δ1) have also been shown to be specific cargo receptors of G-protein-coupled receptors and differentially control G-protein-coupled receptor trafficking in the biosynthetic pathway of astrocytes (87). The binding of p24 proteins to chimaerins, a family of phorbol ester/diacylglycerol receptors (88), and T1/ST2, a receptor-like molecule homologous to the type I interleukin receptor (16), implicates p24 protein in the trafficking of these receptors. In addition, p24 proteins modulate the trafficking and metabolism of amyloid-β precursor protein, a transmembrane protein linked to Alzheimer's disease (34). Furthermore, p24 proteins have been shown to bind and modulate the activity of the γ-secretase complex that mediates the cleavage of amyloid-β precursor protein (89).

In summary, it seems certain that one of the direct functions of p24 proteins is cargo protein selection in both the anterograde and retrograde pathways of the early secretory pathway and that undoubtedly, additional secretory proteins will be discovered that require p24 protein function for normal secretion.

Additional potentially indirect functions

In view of the fact that p24 proteins are required for COPI vesicle biogenesis, as well as for the efficient transport of a growing list of secretory proteins, it is expected that perturbing normal p24 function would affect the general functioning of the early secretory pathway. Thus, it is likely that p24 function is required to maintain and supply the protein machinery

for normal secretory pathway function as has been suggested recently (8). Thus, perturbation of normal p24 family member distribution causes disruption of secretory pathway morphology and function in several systems. In melanotrope cells of the amphibian *X. laevis*, expression of p24α3-GFP transgene resulted in the fragmentation of the Golgi and in the formation of ER-localized electron-dense structures in which cargo molecules accumulated (37). In mammalian cell lines, overexpression of p24 proteins induced the expansion of ER membranes and the fragmentation of the Golgi (29, 90, 91) and overexpression in neurons causes severe neurological problems in mice (92). Conversely, knockdown of p25/p24α2 by single-interfering RNA also caused fragmentation of the Golgi (93), and cells from heterozygous p23/p24δ1 knockout mice showed dilation of Golgi saccules (31). These studies clearly indicate that the manipulation of p24 expression alters membrane dynamics in the early secretory pathway, although the mechanism behind these effects is unclear given that the perturbation of p24 function may perturb the normal function of potentially numerous proteins that transit or cycle in the secretory pathway.

In addition, p24 protein function has been proposed in the ER quality control of certain secretory proteins by preventing misfolded or aberrant proteins from exiting the ER and traversing the secretory pathway (10, 34, 67), and p24 proteins are proposed to function in folding or other types of posttranslational modification (49). Again, these effects are likely to be indirect due to possible perturbation in multiple proteins. This is highlighted by the fact that the depletion of p24 proteins can cause activation of the unfolded protein response in some situations and thus impact overall ER function (94).

Post-Golgi and other functions

Some studies have indicated that p24 proteins may also have post-Golgi functions. gp25L2/p24α2 and Tmp21-I/p24δ1 have been found in *trans*-Golgi network-derived vesicles (95). A small fraction of p23/p24δ1 is localized to secretory granules in pancreatic β cells (40), and p23/p24δ1 has been reported to localize to plasma membrane in some cell types (39, 96). Interestingly, p23/p24δ1 has been detected in complexes with the plasma membrane protease presenilin and found to alter γ-secretase, activity (96). In addition, it has been shown that p24 proteins associate with peroxisomes and play a role in peroxisome fission and inheritance (44).

Summary/conclusions and outlook

Protein secretion plays a fundamental role in numerous biological processes. The proper functioning of the secretory pathway requires various events to proceed normally, such as efficient protein transport from the ER and retrieval of escaped cargo and recycling of essential components via the retrograde pathway. The p24 proteins are central to these

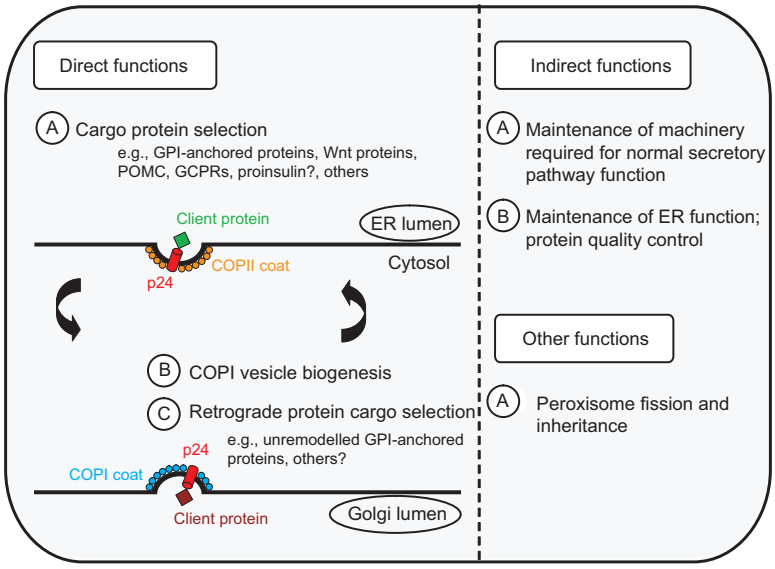

Figure 2 Direct and indirect functions for p24 proteins in eukaryotic cells.
The p24 family of proteins is localized principally to the early secretory pathway and has been shown to be required for the normal ER export (secretion) of various secretory proteins. This cargo selection function involves interaction of the luminal domain of p24 with selected cargo proteins in the ER and interaction of the cytosolic domain with the COPII coat, thus efficiently delivering the cargo into the budding transport vesicle. Once these vesicles fuse with the intermediate compartment (not shown) or *cis*-Golgi, p24 proteins are required for the formation of retrograde-targeted COPI vesicles. In the retrograde pathway, p24 function is required for the biogenesis of COPI-coated vesicles, as well as potential cargo selection for proteins that need to be recycled back to the ER. These are direct functions of p24 proteins, which require p24 protein oligomerization. Given that p24 protein function is required for the secretion and potential retrograde transport of multiple proteins, p24 proteins are thus important components for the process of secretion and protein quality control in general (indirect functions). COPI, coat protein complex I; COPII, coat protein complex II; ER, endoplasmic reticulum.

processes, particularly in multicellular metazoan cells. A number of recent studies have added to the growing list of secretory cargo proteins that depend on p24 proteins for efficient transport, and this list is certain to increase in the future. The central role of p24 proteins in the secretory pathway has also identified that the modulation of p24 function impacts this pathway although such effects may be indirect (Figure 2).

The challenge going forward will be to identify further the specific protein cargo that requires p24 protein function, as well as the role of lipid binding of the p24 proteins recently identified. The regulation of p24 protein oligomerization and incorporation into COPI and COPII vesicles is another area for further research. Some p24 proteins contain putative phosphorylation sites in their cytosolic domains (see Supplementary Table 1) that could affect these properties. Furthermore, the specific pattern of expression indicates that p24 proteins in multicellular organisms may have important cell-specific functions. Tissue-specific knockouts of p24 proteins may shed some insight into particular roles in various tissues. Of course, a caveat of such experiments may be that knockout may have both direct and indirect effects due to the general role of these proteins in COPI vesicle formation and facilitating the normal transport of multiple proteins in the early secretory pathway.

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