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Intracellular trafficking of P-glycoprotein

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Abstract

Overexpression of P-glycoprotein (P-gp) is a major cause of multidrug resistance in cancer. P-gp is mainly localized in the plasma membrane and can efflux structurally and chemically unrelated substrates, including anticancer drugs. P-gp is also localized in intracellular compartments, such as ER, Golgi, endosomes and lysosomes, and cycles between endosomal compartments and the plasma membrane in a microtubular-actin dependent manner. Intracellular trafficking pathways for P-gp and participation of different Rab proteins depend on cellular polarization and choice of primary culture, cell line or neoplasm. Interruption of P-gp trafficking to the plasma membrane increases intracellular P-gp accumulation and anticancer drug levels, suggesting a potential approach to overcome P-gp-mediated multidrug resistance in cancer.

Keywords

P-glycoprotein; localization; trafficking; recycling; multidrug resistance

1. Introduction

P-glycoprotein (permeability glycoprotein, P-gp) is a 170KDa membrane protein which belongs to sub-family B of the ATP-binding cassette (ABC) transporter superfamily. P-gp (also designated ABCB1) is encoded by the ABCB1 or MDR1 (multidrug resistance 1) gene in humans (Chen et al., 1986). Human P-gp is composed of 1280 amino acids and has two halves. The N-terminal half contains 6 transmembrane domains, followed by a large cytoplasmic domain with an ATP-binding site. The second half also has 6 transmembrane domains and an ATP-binding site. A flexible linker connects both halves. Three glycosylation sites are located on the first extracytoplasmic domain (Figure 1). There is 65% sequence homology between the two halves (Chen et al., 1986). P-gp utilizes ATP hydrolysis to transport a wide range of chemically and structurally unrelated substrates, including hydrophobic, amphipathic natural product drugs, structurally unrelated anticancer reagents and HIV-protease inhibitors (Lee et al., 1998).

2. Expression and biological function

P-gp is mainly found in the gastrointestinal tract, liver, kidney and blood brain barrier. In the small intestine, P-gp is located in the apical membrane of mucosal cells, enabling its excretion of toxins and protection of the organism (Thiebaut et al., 1987). In kidney, P-gp is

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located on the brush border of proximal tubule cells and in hepatocytes, P-gp resides in the canalicular apical domain. These localization sites permit excretion of xenobiotics and endogenous metabolites into the urine and bile (Schinkel et al., 1997). An important localization of P-gp is on the luminal surface of capillary endothelial cells of the blood brain barrier which prevents penetration of cytotoxins through the endothelium. In *mdr1a/mdr1b* knock out mice, tissue concentrations of P-gp substrates are higher than in normal mice, suggesting that P-gp plays a role in determining oral drug bioavailability (Schinkel et al., 1997).

In clinical oncology, overexpression of P-gp is an important and well-studied mechanism of multidrug resistance (MDR). About half of human cancers express P-gp at levels sufficient to confer multidrug resistance. Cancers from liver, intestine and kidney exhibit high endogenous P-gp levels even before the chemotherapy. P-gp expression is present in one-third of patients with acute myelogenous leukaemia at the time of diagnosis, and more than 50% of patients at relapse (Han et al., 2000). Association between P-gp expression and poor outcome of treatment with substrate drugs is well established in several hematopoietic cancers (Sikic, 1999). There is a greater likelihood of treatment failure if P-gp expression increases after therapy.

3. Intracellular localization of P-gp

Confocal microscopy studies of polarized and nonpolarized cells reveal that P-gp is localized in the plasma membrane and intracellularly in endoplasmic reticulum (ER), Golgi, various endosomes, lysosomes (Sai et al. 1999, Fu et al, 2004, Fu and Roufogalis, 2007). Although mitochondria localization of P-gp was reported (Munteanu et al., 2006), co-localization of P-gp-EGFP or wild-type P-gp with mitochondrial marker were not observed (Fu et al., 2007, Paterson and Gottesman, 2007). The sites of P-gp synthesis (ER), modification (Golgi), trafficking/recycling (endosomes) and degradation (lysosome, co-localized with LAMP1/2) are indicated in Figure 2. In addition, P-gp can be ubiquitinated and degraded in the proteasome (Zhang et al., 2004). Study in HeLa cells transiently expressing P-gp-EGFP showed that ER localization is transient suggesting that P-gp rapidly departs the ER after synthesis (Fu et al., 2004). In stable expressing MCF-7 cells, P-gp-EGFP did not co-localize with Rab11 positive recycling endosomes and 57% of intracellular P-gp-EGFP co-localized with EEA1 positive early endosome (Fu and Roufogalis, 2007). However, in polarized WIFB9 cells, P-gp cycled in Rab11a endosomes between the recycling endosome pool and the apical plasma membrane (Sai et al. 1999).

4. Intracellular traffic of P-gp

4.1 Synthesis and folding in ER

The ER is the starting point for newly synthesised proteins to enter the secretory pathway. The ER lumen contains folding factors and molecular chaperones. Chaperones such as calnexin, calreticulin, Hsc70 (heat shock cognate 71 kDa protein) and ERp57 are specifically glycoprotein relevant (High et al., 2000). P-gp is synthesized as a 150 kDa core-glycosylated intermediate protein, and is associated with calnexin and Hsc70 during folding (Gething and Sambrook, 1992). Misfolded P-gp can be rapidly degraded (Loo and Clarke 1997), and degradation of misfolded proteins is proteasome-mediated (Goldberg, 2003), presumably by ERAD (ER associated protein degradation). P-gp substrates, such as cyclosporin A, rescue misfolded P-gp (Loo and Clarke, 1997). These substrates bind the drug-binding sites and facilitate conversion of misfolded intermediates into 'near native' conformation, which can escape the cell's quality control mechanism (Loo and Clarke, 1997).

4.2 From ER to Golgi

After correct folding in ER, the 150 kDa P-gp moves to the Golgi for further glycosylation as a 170 kDa mature protein (Molinari et al., 1994). It is not clear which transport signals mediate P-gp movement from ER to Golgi. Coat protein II regulates ABCA1 and CFTR (ABCC7) traffic from ER to Golgi (Tanaka et al., 2008, Ameen et al., 2007). SPTLC1 (Serine palmitoyltransferase enzyme 1) interacts with ABCA1 in ER resulting in ER retention, suggesting that SPTLC1 may regulate ABCA1 ER exit (Tamehiro et al., 2008). The Golgi also plays a major role in the biosynthesis of glycolipids, the glycan chains of glycoproteins. The *cis*-Golgi network, which is possibly equivalent to the ER-Golgi intermediate compartment, receives newly synthesized proteins from the ER, whereas post-translational modifications occur in the *trans*-Golgi network (TGN). Microtubules are required for ER-Golgi traffic (Presley et al., 1997). How microtubules regulate P-gp traffic from ER to Golgi has not been described. TGN is a major sorting station for proteins destined for the plasma membrane and endocytic pathway. The sorting mechanism for P-gp is unknown. Membrane proteins can use N-glycan chains as sorting determinants (Keller and Simons, 1997) which may occur with P-gp. However, other studies suggest that N-glycosylation at 596 is not essential for ABCG2 trafficking (Diop and Hrycyna, 2005). Immature core-glycosylated CFTR (ABCC7) can traffic to the plasma membrane via an unconventional pathway and is functional (Gee et al., 2011).

4.3 From Golgi to cell membrane

Newly synthesized membrane proteins can be delivered to the plasma membrane in different ways. The constitutive/default pathway involves membrane protein incorporation into vesicles which move directly to the plasma membrane along the cytoskeleton (Kipp and Arias 2000). The second pathway is via an intracellular endosomal system in which protein-containing vesicles are transported to endosomal compartments to form an intracellular pool, followed by further transport to the plasma membrane (Sai et al., 1999). The cytoskeleton is involved in all traffic of membrane protein vesicles (Musch et al., 1997).

In nonpolarized human cancer cells, P-gp is co-localized with EEA1 and Rab5 positive early endosomes suggesting that P-gp traffic to the plasma membrane involves the endosomal pathway (Fu and Roufogalis, 2007). Pulse-labeling studies in rats (Kipp and Arias, 2000) and imaging studies in polarized WIF-B cells showed that *mdr1*-GFP is directly transported from Golgi to the cell membrane. In nonpolarized WIF-B9 cells, basolateral proteins or transcytosis proteins localized to the plasma membrane, whereas apical ABC transporter (BSEP or P-gp) were restricted to *rab11a*-positive endosomes intracellular sites, and traffic directly to the apical membrane when polarization is established (Wakabayashi et al., 2005). Live cell imaging revealed a role for large *Rab11a*-containing tubular vesicles in movement of *mdr1*-GFP from TGN to plasma membrane (Sai et al., 1999). P-gp-EGFP tubular vesicles structures were also observed in nonpolarized MCF-7 cells which expressed P-gp-EGFP, however, they co-localized with EEA1 or Rab5 positive early endosomes (Fu and Roufogalis, 2007) (Figure 2). In both non-polarized and polarized cells, P-gp can traffic to the plasma membrane (or apical domain) directly or indirectly via an intracellular endosome pool. In polarized cells, the intracellular pool is the *Rab11a* positive recycling endosome.

4.4 Endocytosis, Recycling and role of Rab GTPases

Pulse-chase and anti-P-gp antibody, studies showed that P-gp undergoes endocytosis and cycling between the intracellular pool and the plasma membrane (Kim et al., 1997). Actin but not microtubule disruption resulted in extensive intracellular EEA1-positive endosomal P-gp-EGFP accumulation, suggesting that actin may play a role in P-gp-EGFP trafficking/cycling between the endosomal pool and the plasma membrane (Fu and Roufogalis, 2007).

P-gp associates with actin through ezrin, radixin and moesin, and disrupting the association increases intracellular P-gp and drug sensitivity in leukemia cells (Luciani et al., 2002).

Rab GTPases regulate protein trafficking and recycling, and are associated with organelles or pathways of the vesicle transport system (Somsel Rodman and Wandinger-Ness, 2000). Rab1, 2 and 6 are localized in ER and Golgi and regulate vesicle transport along the biosynthetic pathway, whereas Rab4 and 5 are mainly located in early endosomes and regulate early steps of the endocytic process, indicating endosome-endosome fusion.

Simultaneous expression of P-gp-EGFP and dominant-negative Rab5 (S34N-Rab5) in HeLa cells resulted in large intracellular accumulation of P-gp-EGFP in TfR positive recycling endosomes. Similarly, increased intracellular wild type P-gp was also observed in multidrug resistant MCF-7/Adr cells transfected with Rab5-S34N, suggesting that Rab5 regulates P-gp traffic from the endosome compartment to the plasma membrane in nonpolarized cells (Fu et al., 2007). However, studies in LS174T cells, showed that overexpression of Rab5 resulted in removal of P-gp from the plasma membrane into intracellular compartments, suggesting that Rab5 regulates P-gp endocytosis in these cells (Kim et al., 1997). Rab5 appears to have a different role in P-gp trafficking/cycling in different cancer cells and cell lines. Notably, whereas P-gp recycles between the plasma membrane and Rab5 positive early endosome in non-polarized cancer cells, it recycles between the apical membrane and a Rab11a positive recycling endosome pool in the polarized cells.

In drug resistant leukemia cells, K562ADR, overexpression of GFP-Rab4 or constitutively active Rab4Q72L mutant, but not dominant negative Rab4S27N mutant, decreased the presence of P-gp in the cell surface, suggesting that, in these cells, Rab4 regulates exocytotic P-gp trafficking to the plasma membrane from intracellular compartments (Ferrández-Huertas et al., 2011). However, in HeLa cells, overexpression of wild-type Rab4 and dominant negative mutant N121I-Rab4 did not change the intracellular distribution of P-gp-EGFP after cotransfection with P-gp-EGFP plasmid. The different results are possibly due to the different cell lines used in these studies.

Another small GTPase, RalA, participates in receptor-mediated endocytosis and regulated exocytosis. Co-expression of P-gp-EGFP and constitutively active RalA-G23V but not dominant-negative RalA-S28N in HeLa cells resulted in intracellular accumulation of P-gp-EGFP in approximately 72 % of cells (Fu et al., 2007). In addition, wild type P-gp was redistributed from the plasma membrane into an intracellular compartment in multidrug resistant MCF-7/Adr cells transfected with RalA-G23V (Fu et al., 2007), suggesting that RalA could either increased rate of endocytosis or inhibition of recycling of P-gp-EGFP.

The role of Rab proteins in P-gp trafficking and cycling is unclear. Rab11 is important for apical recycling endosomes in polarized epithelial cells. In polarized WIF-B cells, BSEP (Bile Salt Export Pump) cycles between Rab11 positive endosome and the apical membrane (Wakabayashi et al., 2005). Rab11 also regulates apical recycling of CFTR in polarized intestinal epithelial cells (Silvis et al., 2009). However, in non-polarized MCF-7 cells, stable expressed P-gp-EGFP did not co-localize with Rab11 positive recycling endosome. Participation of different components of the endosomal trafficking system depends on the polarization status of the cell. In addition, Rab17, 18, 20 and 25, also facilitate endocytosis (Takai et al., 2001). Further studies are needed to investigate the role of Rab proteins in P-gp trafficking.

Rab proteins interact with microtubules and/or actin based motor proteins for their effects on endocytic transport. Rab5 and its effectors bind to actin (Kato et al., 1996). Interactions between Rab8 protein and actin cytoskeleton are critical for vesicle docking and fusion (Peranen et al., 1996). Rab5 or Rab6 interact with microtubule associated motor protein,

such as kinesin, Rabkinesin-6 (Nielsen et al., 1999, Echard et al., 1998). Rab7 and Rab9 control of endocytic vesicle transport depends on microtubules and dynein (Somsel Rodman and Wandinger-Ness, 2000). In hepatocytes, myosin Vb is involved in BSEP traffic from Rab11a-endosomes to the apical membrane (Wakabayashi et al., 2005).

Inhibitors are used to study protein trafficking and endocytosis. Brefeldin A inhibits proteins traffic from ER to Golgi. Concanamycin A and destruxin B inhibit V-ATPases which is important for organelle acidification and protein trafficking. Mycophenolic acid, an inhibitor of GTP synthesis, also can inhibit protein trafficking (Muroi and Takatsuki, 2001). In addition, endocytosis inhibitors, such as chlorpromazine, monodansylcadaverine, methyl- β -cyclodextrin, nystatin and dynasore, are used to study endocytosis/recycling (Ivanov, 2008). Furthermore, cytoskeleton inhibitors, such as nocodazole and cytochalasin, are also widely used to study protein trafficking.

5. Clinical implications

Blocking P-gp traffic to the plasma membrane result in intracellular accumulation of P-gp. Inhibition of P-gp maturation (by proteasome inhibitor) resulted in accumulation of inactive P-gp in Golgi (Loo and Clarke, 1999). It is possible that intracellular P-gp trapped between Golgi and the plasma membrane is in an active form, but does not contribute to drug resistance (Duensing and Slate, 1994, Larsen et al., 2000). Inhibition of P-gp traffic to the plasma membrane increases intracellular P-gp accumulation and decreases anticancer drug levels thus rendering P-gp positive cells more sensitive to anticancer drugs (Fu et al., 2004, 2007). Interruption of P-gp traffic may provide a new strategy to overcome MDR in cancer. To identify specific therapeutic sites, studies are needed to understand molecular and cellular mechanisms of P-gp intracellular traffic/cycling and regulatory targets. These mechanisms differ depending on cellular polarization and the cell type being studied. Generalizations based on studies performed in single cell types should be interpreted with caution.

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Figure 1.
Model of P-gp structure: (TM—transmembrane domain).

Figure 2.
Generic model of cellular localization of P-gp and possible traffic/cycling routes.