When intracellular logistics fails – genetic defects in membrane trafficking

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Summary

The number of human genetic disorders shown to be due to defects in membrane trafficking has greatly increased during the past five years. Defects have been identified in components involved in sorting of cargo into transport carriers, vesicle budding and scission, movement of vesicles along cytoskeletal tracks, as well as in vesicle tethering, docking and fusion at the target membrane. The nervous system is extremely sensitive to such disturbances of the membrane trafficking machinery, and the majority of these disorders display neurological defects – particularly diseases affecting the motility of transport carriers along cytoskeletal tracks. In several disorders, defects in a component that represents a fundamental part of the trafficking machinery fail to cause global transport defects but result in symptoms limited to specific cell types and transport events; this apparently reflects the redundancy of the transport apparatus. In groups of closely related diseases such as Hermansky-Pudlak and Griscelli syndromes, identification of the underlying gene defects has revealed groups of genes in which mutations lead to similar phenotypic consequences. New functionally linked trafficking components and regulatory mechanisms have thus been discovered. Studies of the gene defects in trafficking disorders therefore not only open avenues for new therapeutic approaches but also significantly contribute to our knowledge of the fundamental mechanisms of intracellular membrane transport.

Key words: Disease, Disorder, Genetic, Membrane trafficking, Vesicle transport

Introduction

One of the major processes responsible for the correct localization of molecules within the cell is called membrane trafficking or vesicular transport. Here, membraneous carrier structures, which can be small vesicles or larger tubular or saccular elements, bud off a donor compartment and fuse with a recipient one, thus delivering their membrane-associated and soluble lumenal constituents to the target organelle. The major cellular routes of membrane trafficking are the biosynthetic pathway responsible for the transport of proteins synthesized in the endoplasmic reticulum to the extracellular space, or to other cellular membrane compartments, and the endocytic pathway responsible for the uptake of compounds from the extracellular milieu to be used for cellular metabolism.

Most membrane and secretory proteins, as well as many lipids, are synthesized in the endoplasmic reticulum, whose luminal environment is especially suited to facilitate the proper folding of the synthesized proteins and the initial steps of N-linked glycosylation. Proteins that are destined for transport out of the ER move on to the Golgi complex, where they obtain further post-translational modifications. Subsequently, the proteins are sorted for different destinations: the plasma membrane, regulated secretory granules or vesicles, or organelles of the endocytic pathway (Bard and Malhotra, 2006; McNiven and Thompson, 2006). This anterograde flow is counterbalanced by retrograde trafficking, which is essential for the maintenance of organelle homeostasis and re-use of components of the trafficking machineries (Sannerud et al., 2003). Within the endocytic pathway, the internalized molecules are also efficiently sorted: selected molecules are returned to the cell surface (e.g. recycling receptors), whereas others (e.g. receptors to be downregulated or compounds to be degraded) are transported to late endosomes and lysosomes, which are responsible for the degradation of internalized material (Maxfield and McGraw, 2004). The out-going and in-coming trafficking pathways communicate through bidirectional transport between the Golgi complex and endosomes (Bonifacino and Rojas, 2006).

In principle, the consecutive steps in the vesicle-mediated exchange of material consist of the same stages irrespective of the particular donor and acceptor membranes in question. These stages include sorting of proteins and lipids, formation of transport carriers, movement of the vesicles along cytoskeletal filaments, recognition of the target organelle, and fusion of the vesicles with the acceptor compartment (Bonifacino and Glick, 2004).

Cell biologists view the molecular machinery that drives intracellular membrane trafficking as a central molecular network that maintains cell viability and organelle functionality and, as such, a key area of basic research. Since the 1990s, an increasing number of human inherited disorders have been shown to be due to defects in genes encoding components of this apparatus. This has provided us with useful arguments in grant applications. However, one should not underestimate the additional value of such research. It not only helps us to understand the molecular mechanisms underlying

specific inherited diseases but also provides insight into the function of the transport apparatus in the context of the entire mammalian organism. (1) It specifies in which cell- or tissue-specific processes a given component forms a 'critical point'. (2) It yields insight into the functional redundancy in the transport apparatus. (3) It gives us an idea of the compensatory mechanisms that could alleviate the consequences of a defect.

Seven years ago, we surveyed the known genetic disorders of the membrane transport machinery (Olkkonen and Ikonen, 2000). These were then restricted to disorders affecting well-established components of the trafficking machinery or disorders in which there was good reason to believe that the defective protein belongs to the transport apparatus and the cellular phenotype indicates a trafficking defect. The number of diseases clearly satisfying this definition was then nine. A search of the PubMed and online Mendelian inheritance in man (OMIM) databases using the same criteria now yields 30 diseases or groups of closely related disorders. These can be organized in three categories: defects of the machinery responsible for cargo sorting and transport vesicle formation (Table 1, Category A); disorders that disturb the movement of transport carriers along cytoskeletal tracks (Table 1, Category B); and defects in the tethering, docking and fusion of vesicles at the target membrane (Table 1, Category C). In this Commentary, we concentrate on human diseases studied most at the cell biological level and those representing good examples of how the investigation of disease genes has improved our understanding of intracellular transport. We apologize to researchers whose work is not cited herein owing to the incompleteness of our search method or space limitations.

Defects of the machinery responsible for cargo sorting and transport vesicle biogenesis

In the initial stage of a given membrane transport event, cargo is recruited to specific sites at the limiting membrane of the donor organelle from which transport intermediates bud off. The budding of transport vesicles and the selective incorporation of cargo are both mediated by cytosolic complexes of coat proteins that directly interact with trans-membrane cargo proteins or receptors for luminal cargo molecules. The coat complexes recognize sorting signals in the cytosolic domains of target proteins and deform the membrane to generate convex buds (reviewed by Bonifacino and Glick, 2004). The sorting signals include specific amino acid determinants, saturated fatty acyl moieties, and carbohydrates recognized by lectin-like receptors.

There are two types of inherited disease in which these signals or the machinery that recognizes them is directly affected. Mucolipidosis II (I-cell disease) and related milder disorders, characterized by leakage of multiple lysosomal hydrolases from cells and lysosomal deposits of undegraded material, result from a defect in the sorting of multiple lysosomal proteins. In these diseases, the activity of the Golgi enzyme N-acetylglucosamine-1-phosphotransferase is missing, reduced or altered. The enzyme catalyses the first step in the mannose 6-phosphate (M6P) modification of lysosome-destined proteins, which are recognized in the trans-Golgi network (TGN) or at the cell surface by M6P receptors (MPRs) and routed to lysosomes. The defects in mucolipidosis II and IIIA were recently pinpointed to the gene encoding the α and β subunits of the enzyme (Tiede et al., 2005; Kudo et al., 2006), and that in mucolipidosis IIIC to the gene for the γ subunit of the complex (Raas-Rothschild et al., 2000; Raas-Rothschild et al. 2004). Whereas the above disorders affect the sorting signal on the cargo, proteins acting as cargo receptors are defective in a bleeding syndrome, combined deficiency of coagulation factors V and VIII. In this, the inclusion of the two coagulation factors into ER-Golgi carriers, and thus their secretion, is hampered by defects in ERGIC-53, a mannose-binding lectin that executes a cargo-sorting function in ER-to-Golgi trafficking (Nichols et al., 1998), or its binding partner, multiple coagulation factor deficiency protein 2 (MCFD2) (Zhang et al., 2003; Zhang et al., 2006). The patients have normal plasma concentrations of other proteins, which suggests that the Ca^{2+}-dependent ERGIC-53–MCFD2 complex has a specific function in sorting of a subgroup of glycoproteins that are transported out of the ER (Zhang et al., 2005). Note that, by analogy with the above examples, one could also include in this category defects in cell surface receptors or adaptor proteins involved in the endocytosis of specific ligands – for example, LDL receptors in familial hypercholesterolemia (FH), which leads to impaired cellular LDL uptake and dramatically increased serum LDL-cholesterol levels. However, owing to space limitations we do not discuss these disorders here.

Arf/Sar GTPases

Small Sar GTPases play central roles in COPII coat assembly and cargo selection at ER exit sites, and the related ARF GTPases function in the recruitment of COPI coats and clathrin/adaptor protein complexes at the Golgi, endosomes and plasma membrane (reviewed by Bonifacino and Glick, 2004; Behnia and Munro, 2005; D'Souza-Schorey and Chavrier, 2006). A striking example of a cargo-inclusion defect due to disturbed coat assembly is provided by chylomicron retention disease (CMRD) and related severe disorders of fat malabsorption. In these disorders, enterocytes fail to secrete lipids derived from the diet into the circulation in the form of chylomicrons, owing to mutations in the gene encoding Sar1b (Jones et al., 2003). The most common genetic defects in the CMRD families are missense mutations that affect residues in the highly conserved guanine-nucleotide-binding motifs of Sar1b. The enterocytes of CMRD patients display chylomicron-like particles in dilated and vesiculated channels of the smooth ER and in huge membrane-bound compartments. Studies by Siddiqi et al. suggest that chylomicrons are included into large ER-to-Golgi carriers ranging in diameter from 350 nm to 500 nm (pre-chylomicron transport vesicles) distinct from the COPII-coated vesicles formed at conventional ER exit sites (Siddiqi et al., 2003). Even though it is not definitely established that chylomicrons leave the ER in COPII-coated carriers, GTP binding and/or hydrolysis by Sar1b seems to play an essential role in chylomicron transport from the ER to the Golgi (reviewed by Shoulders et al., 2004). The fact that Sar1b defects lead to a phenotype restricted to chylomicron secretion and fail to cause global secretory defects is presumably due to the presence of a fully functional Sar1a isoform, which enables near-normal function of the secretory pathway in the majority of the patients' cells. The Sar1b isoform probably interacts with specific ER subdomains employed in the sorting and transport of nascent chylomicrons.

Recently, cranio-lenticulo-sutural dysplasia (CLSD), a disease characterized by facial dysmorphisms and skeletal defects, was shown to result from a defect in the COPII coat subunit SEC23A (Boyadjiev et al., 2006). This protein functions in the same transport step as Sar1, cargo export from the ER, and acts as a GTPase-activating protein (GAP) for Sar1 (Barlowe et al., 1994; Antonny and Schekman, 2001; Bonifacino and Glick, 2004). Consistent with an ER export defect, gross dilatation of the ER was observed in patient fibroblasts (Boyadjiev et al., 2006). Furthermore, Lang et al. showed in zebrafish *crusher* mutant chondrocytes with an orthologous *sec23a* defect that proteins accumulate in a distended ER, which results in a severe reduction in cartilage extracellular matrix deposits (Lang et al., 2006). The dysfunction in CLSD resembles that in CMRD, displaying an ER export defect that results in limited disease symptoms in specific cell types. As in the case of Sar1, humans have two paralogous *SEC23* genes, of which one is apparently sufficient to carry out a minimal essential ER export function.

Another disorder caused by a defect in small GTPases responsible for coat recruitment is periventricular heterotopia with microcephaly, a syndrome characterized by severe developmental defects of the central nervous system (CNS). Here, the defect has been pinpointed to a guanine nucleotide exchange factor (GEF) for ARF GTPases, ARFGEF2 (Sheen et al., 2004). This protein facilitates GDP-GTP exchange on the GTPase, a process associated with membrane attachment and activation of its coat-recruitment function. ARFGEF2 has been implicated in both ER-to-Golgi and post-Golgi transport; a specific role has been suggested for it in the transport of γ-aminobutyric acid (GABA) type-A receptor (Charych et al., 2004) and the actin-binding protein filamin A (Lu et al., 2006). Furthermore, ARFGEF2 interacts with Exo70, a protein involved in late exocytic events (Xu et al., 2005). Inhibition of ARFGEF2 prevents the Golgi-to-cell-surface transport of molecules such as E-cadherin and β-catenin, which suggests that disturbance of vesicle transport through the secretory pathway causes the defects in neuronal proliferation and migration observed in patients (Sheen et al., 2004). In periventricular heterotopia, the major symptoms occur in the CNS, and global secretory defects are not observed. This is probably again because mammalian cells have a number of ARFGEFs (reviewed by Mouratou et al., 2005), and a defect in one only has limited functional consequences.

Membrane lipids

During the past few years, an important role of specific membrane lipids in the recruitment of coat complexes has emerged. A lipid class with major impact on membrane trafficking is the phosphoinositides (PI). The majority of PI are constitutively present in cells and are generally found only on a small subset of organelles; PtsIns(3,4)P_2 and PtdIns(3,4,5)P_3 are second messengers synthesized in response to external signals (reviewed by Downes et al., 2005; Halstead et al., 2005). PtdIns(4,5)P_2 has several pivotal functions in the cell: (1) it serves as substrate for powerful signal-generating enzymes, PI-phospholipase C and type I PI 3-kinases; (2) it is a crucial regulator of the actin cytoskeleton; and (3) it plays a central role in clathrin-mediated endocytosis by recruiting a number of accessory proteins, such as the adapter protein (AP) AP-2, epsin, AP180 and dynamin.

In Lowe oculocerebrorenal syndrome, a protein called OCRL1, a polyphosphoinositide 5-phosphatase, is defective (Attree et al., 1992; Zhang et al., 1995; Suchy et al., 1995). This leads to cellular accumulation of PtdIns(4,5)P_2, which induces aberrations in both membrane trafficking and the actin cytoskeleton. OCRL1 localizes to early endosomes and the TGN and is enriched in clathrin-coated transport intermediates. OCRL1 can interact directly with clathrin heavy chain and promote clathrin assembly in vitro (Ungewickell et al., 2004; Choudhury et al., 2005). Furthermore, recent evidence suggests that Rab GTPases regulate both the phosphatase activity and membrane targeting of OCRL1 (Hyvola et al., 2006). Depletion of OCRL1 induces redistribution of the cation-independent MPR to early endosomes, which suggests it has a function in transport from endosomes to the TGN, probably in the recruitment/regulation of trafficking machinery on the endosome membranes (Choudhury et al., 2005). Thus, a defect in transport between endosomes and the TGN, which is consistent with the abnormal secretion of lysosomal hydrolases observed in patients with Lowe syndrome, is likely to contribute to the pathology of the disease.

Hermansky-Pudlak syndrome

Another interesting group of disorders that exhibit defects in the generation of transport intermediates is Hermansky-Pudlak syndrome (HPS), a cluster of diseases characterized by defective biogenesis of lysosome-related organelles (reviewed by Wei, 2006). In HPS2, the disease-causing mutations are in a gene encoding the β1 subunit of AP-3 (Dell'Angelica et al., 1999). In HPS type 1 and types 3-8, the defects have been pinpointed to subunits of three distinct protein assemblies: biogenesis of lysosome-related organelles complex (BLOC) 1, BLOC2 and BLOC3 (reviewed by Di Pietro and Dell'Angelica, 2005; Gautam et al., 2006) (see Fig. 1). In addition, the mouse models for HPS include animals with mutations in the Sec1-Munc18 protein VPS33A, the small GTPase Rab38, the AP-3δ subunit, Rab geranylgeranyl-transferase (RGGT) and several additional components of the BLOC1 complex.

The mammalian AP-3 complex decorates budding profiles on early-endosome-associated tubules (Peden et al., 2004), and evidence suggests the complex functions in the transport of integral membrane proteins to late endocytic compartments (reviewed by Robinson and Bonifacino, 2001; Ohno, 2006). In melanocytes, AP-3 is required for the transport of tyrosinase to maturing melanosomes (Huizing et al., 2001). It also appears to play a role in the movement of lytic granules of NK cells and cytotoxic T-lymphocytes (CTLs); the granules in CTLs from HPS2 patients are enlarged and fail to move towards the microtubule-organizing center upon stimulation (Clark et al., 2003). Therefore, AP-3 could participate in the trafficking and correct localization of proteins that attach lytic granules to microtubules.

Our understanding of the cellular functions of the BLOC complexes is limited; they were assumed to function in the biogenesis of lysosome-related organelles. However, there is also experimental evidence for their involvement in LAMP-3 and tyrosinase-related protein-1 trafficking in melanocytes, as well as in the perinuclear clustering of late endocytic compartments in fibroblasts (Boissy et al., 1998; Nazarian et al., 2003; Huizing et al., 2004). The cell biological

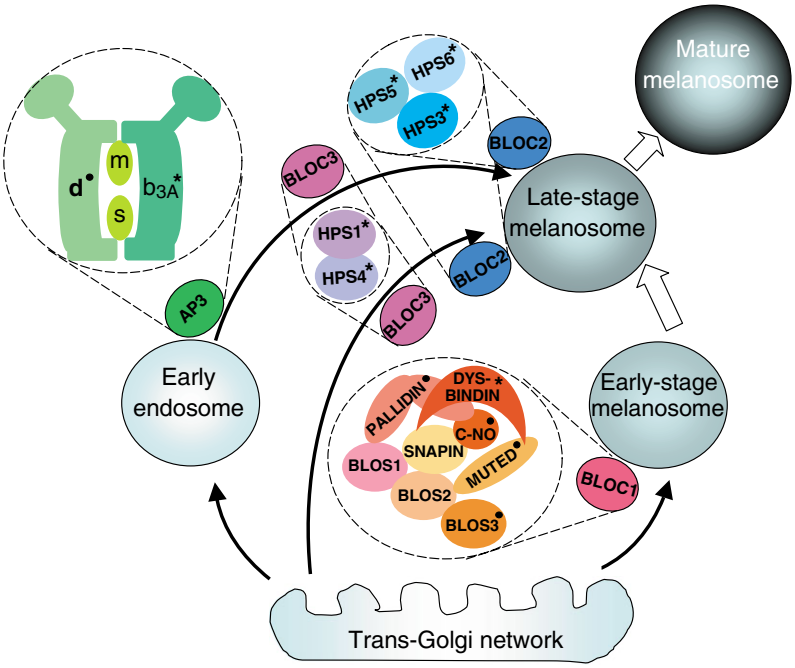

Fig. 1. Model for the role of HPS proteins in melanosome biogenesis. The lysosome-related organelle complexes 1, 2 and 3 (BLOC1-BLOC3) and their subunits are schematically illustrated. Solid arrows indicate cargo proteins being targeted to melanosomes and open arrows illustrate organelle maturation. BLOC1 is implicated in the targeting and fusion of trans-Golgi-network-derived vesicles with early-stage melanosomes; BLOC2 may mediate targeting/docking/fusion of vesicles with more mature melanosomes. Some proteins are transported to melanosomes via early endosomes through AP-3- and BLOC3-dependent processes. Components with identified disease mutations in both humans and mice are indicated by * and those with mouse mutations only by ●. d, δ-subunit; m, μ3-subunit; s, σ3-subunit; b3A, β3A-subunit.

consequences of the genetically heterogeneous group of HPS disorders are strikingly similar: the same group of specialized lysosome-related organelles (melanosomes, platelet-dense granules, lamellar bodies of type II alveolar epithelial cells, T-lymphocyte lytic granules) is affected by defects in a large number of different protein components. Therefore, HPS and its mouse models have provided valuable functional clues and a toolbox of proteins the detailed analysis of which will facilitate comprehensive understanding of the biogenesis of these organelles.

Dynamins

Dynamins are large GTPases that were first characterized as mediators of clathrin-coated vesicle fission from the plasma membrane (reviewed by Danino and Hinshaw, 2001). Defects in the gene encoding dynamin 2, a ubiquitously expressed dynamin variant, cause two inherited disorders: centronuclear myopathy (Bitoun et al., 2005) and the dominant, intermediate B form of Charcot-Marie-Tooth disease (CMTDIB) (Züchner et al., 2005). Dynamin 2 has been implicated in several cellular functions, including clathrin-dependent endocytosis (Elhamdani et al., 2006), vesicle formation at the TGN (Cao et al., 2005; Kessels et al., 2006), lipid-raft internalization (del Pozo et al., 2005), actin assembly (Schafer et al., 2002; Gomez et al., 2005), and centrosome cohesion (Thompson et al., 2004). Dynamin 2 is expressed in the peripheral nervous system and in the spinal cord, which is relevant for the pathology of Charcot-Marie-Tooth disease (Züchner et al., 2005). In centronuclear myopathy, most of the cellular manifestations, such as centrally located nuclei and a radial arrangement of sarcoplasmic strands around nuclei in extrafusal muscle fibers, may be related to a defect in centrosome function; dynamin 2 has been shown to bind γ-tubulin at the centrosome and to participate in the cohesion of centrosomes and organization of the microtubule cytoskeleton (Thompson et al., 2004). Centronuclear myopathy also involves mild axonal defects in peripheral nerves (Fischer et al., 2006) and, in CMTDIB, the major pathology involves axonal degeneration in the peripheral nervous system (reviewed by Niemann et al., 2006). These neurological defects may be due to disorganization of the microtubule network, which plays a central role in axonal transport, to impaired transport vesicle formation or both. Alternatively, they may reflect defects in glia or other supportive cells, in which dynamin 2 might be the only major dynamin expressed.

Disorders that disturb the motility of transport carriers along cytoskeletal tracks

Cytoskeletal filaments, in particular microtubules and actin, form tracks for transport carriers and play essential roles in determining the subcellular locations of organelles. Microtubules and actin filaments are dynamic structures that have a polarized organization, possessing a fast-growing 'plus end' and an opposite, slow-growing 'minus end'. Motor proteins that drive directional movement of carriers along cytoskeletal filaments are key components of the membrane trafficking apparatus. It is therefore not surprising that genetic defects in motor proteins or components of motor complexes cause several diseases (reviewed by Hirokawa and Takemura, 2003).

Microtubule-based transport

The major motor driving microtubule minus-end-directed movement consists of cytoplasmic dynein and the accessory multiprotein complex dynactin, which increases the processivity of dynein and links cargo to both microtubules and dynein (Schroer, 2004). $p150^{Glued}$ is a central component of dynactin, and point mutations in the *DCTN1* gene encoding this protein have been discovered in neurodegenerative diseases. A G59S point mutation causes lower motor neuron disease (Puls et al., 2003). Furthermore, a subset of patients suffering from amyotrophic lateral sclerosis (ALS) 1 also carry point mutations in DCTN1 (Munch et al., 2004; Munch et al., 2005). Detailed analysis of $p150^{Glued}$ G59S revealed that the mutant protein shows reduced affinity for microtubules and is prone to aggregate, which leads to increased cell death in a motor neuron cell line (Levy et al., 2006). The mutation thus causes both a loss of dynein/dynactin function and a toxic effect. Similar effects are found in mice that have missense mutations in the dynein heavy chain or overexpress the

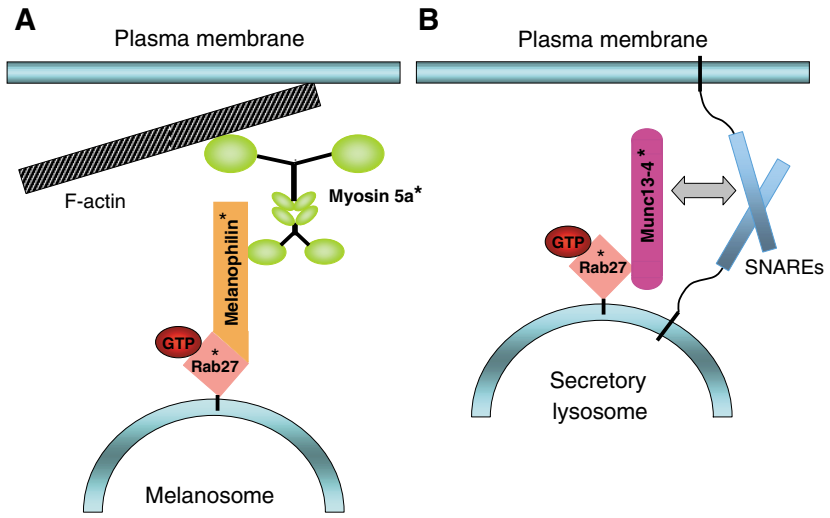

Fig. 2. Rab27a regulates the localization and exocytosis of lysosome-related organelles in different cell types through distinct effector proteins. Mutations in Rab27a and its interaction partners cause several diseases characterized by defects in the subcellular distribution or exocytosis of lysosome-related organelles (A) Pigmentation defects involve mutations in Rab27a, myosin 5a or melanophilin, which bridges the former two proteins. This leads to disturbance of tethering and local movement of melanosomes at the distal actin-rich regions of the melanocyte. (B) Immunological deficits involve defects in Rab27a or its effector Munc13-4. The Rab27a defects disturb the targeting of secretory lysosomes of cytotoxic T-cells to the immunological synapse, whereas Munc13-4 defects apparently disturb the priming of lysosomes for fusion with the plasma membrane. The function of Munc13-4 is thought to be connected with that of the SNARE-based fusion machinery. Components with identified disease mutations are indicated by *.

dynactin component dynamitin. The resulting defects in dynein-dynactin complexes inhibit retrograde axonal transport (LaMonte et al., 2002; Hafezparast et al., 2003). Interestingly, a dynein mutation can rescue axonal transport in an ALS mouse model caused by a mutation in *SOD1* (which encodes superoxide dismutase 1), another gene defective in many human ALS families (Kieran et al., 2005). These findings lend support to the notion that defects in axonal transport are a major cause of neuronal degeneration in ALS and lower motor neuron disease.

Mutations in the small GTPase Rab7 cause a peripheral sensory neuropathy, Charcot-Marie-Tooth disease type 2B (CMT2B) (Verhoeven et al., 2003; Houlden et al., 2004). Rab7 regulates recruitment of dynein/dynactin to endocytic compartments and trafficking in the late endocytic pathway (Press et al., 1998; Jordens et al., 2001; Cantalupo et al., 2001). Importantly, Saxena et al. demonstrated that Rab7 controls the trafficking and neuritogenic signaling of the nerve growth factor (NGF) receptor TrkA, suggesting that Rab7 defects may contribute to neurodegeneration by affecting the transport of neurotrophins or their receptors (Saxena et al., 2005). Another type of Charcot-Marie-Tooth disease, type 2A (CMT2A), is due to a loss-of-function mutation in the motor domain of the plus-end-directed microtubule motor KIF1Bβ (Zhao et al., 2001). Studies of heterozygous *Kif1B*$^{+/-}$ mice revealed that reducing the gene dosage leads to impaired anterograde axonal transport of synaptic vesicle precursors. This reinforces the idea that disturbed axonal transport is a major problem in CMT2A.

Actin-based transport

Defects in actin-based motility have been identified as the cause of Griscelli syndrome (GS), a group of disorders characterized by pigmentation defects (GS1, GS2, GS3), neurological symptoms (GS1), or disturbances of the immunological system (GS2) (see Fig. 2 and Table 1). The disease-causing mutations affect the motor protein myosin 5a (GS1 and GS3) (Pastural et al., 1997; Ménasché et al., 2003), the small GTPase Rab27a (GS2) (Ménasché et al., 2000; Anikster et al., 2002) or a protein called melanophilin or Slac-2 (GS3) (Ménasché et al., 2003). Myosin 5a is essential for the tethering and local movement of melanosomes at the distal actin-rich regions of the melanocyte (Wu et al., 1998 and Fig. 2A). When this mechanism is disturbed, melanosomes accumulate in the central cytoplasm, where they undergo bidirectional movement along microtubules. Rab27a acts as a pivotal component of the myosin 5a receptor on melanosomes (Bahadoran et al., 2001; Wu et al., 2002). The GTPase does not bind myosin 5a directly; the interaction is mediated by melanophilin (Strom et al., 2002; Fukuda et al., 2002).

Rab27a is expressed in cytotoxic T-lymphocytes, and a Rab27a mutation in the *ashen* mouse model leads to a defect in the docking/fusion of lytic granules at the immunological synapse (Stinchcombe et al., 2001), which provides one plausible explanation for the immune deficiency in GS2. Barral et al. have suggested that Rab27b and Rab27a are functionally redundant and that the pathogenesis of GS2 is determined by the relative expression levels of Rab27a and Rab27b in specialized cell types (Barral et al., 2002). The Rab27a defect in GS2 is connected to that in familial hemophagocytic lymphohistiocytosis (FHL) type 3 (see below). The Munc13-4 protein defective in FHL3 is an effector of Rab27a and plays an essential role in the secretion of lysosomes and cytolytic granules (Feldmann et al., 2003; Neeft et al., 2005) (Fig. 2B).

The mechanisms underlying the neurological deficits in GS1 are not well understood. However, there is evidence for a role of myosin 5a in synaptic function: Libby et al. demonstrated that photoreceptor synapses in neurologically affected myosin-Va-mutant mice have both anatomical abnormalities and display aberrant synaptic activity (Libby et al., 2004).

Defects in the tethering, docking and fusion of vesicles at the target membrane

At the final stage of a given membrane trafficking event, a transport carrier reaches its target organelle, docks and eventually fuses with it, releasing its cargo into the compartment and limiting membrane. The initial tethering involves recognition events mediated by large multiprotein assemblies and/or elongated α-helical proteins, which are typically recruited to the transport vesicle and target membranes

Table 1. Summary of membrane trafficking diseases

Disease	Mode of inheritance	Online Mendelian inheritance in man (OMIM) number	Defective protein (gene)	Cellular phenotype	References
Category A					
Centronuclear myopathy	Autosomal dominant	160150	Dynamin 2 GTPase involved in receptor-mediated endocytosis, vesicle formation at the trans-Golgi network and late endosomes, lipid raft internalization, actin assembly and centrosome cohesion (*DNM2*)	Centrally located nuclei in a large number of extrafusal muscle fibers; radial arrangement of sarcoplasmic strands around the central nuclei, predominance and hypotrophy of type 1 fibers; partial arrest of myofiber maturation; suggested defect in centrosome function; mild axonal defects in peripheral nerves	Bitoun et al., 2005; Fischer et al., 2006; Thompson et al., 2004; Schafer et al., 2002; Elhamdani et al., 2006; Cao et al., 2005; Kessels et al., 2006; Gomez et al., 2005; del Pozo et al., 2005; Danino and Hinshaw, 2001
Charcot-Marie-Tooth disease, dominant intermediate B (CMTDIB)	Autosomal dominant	606482	Dynamin 2 See above	Axonal degeneration in peripheral nervous system; myelination defects; suggested axonal transport defects; dynamin-2-mutant forms display decreased membrane association and induce disturbances in microtubule organization	Züchner et al., 2005; Niemann et al., 2006
Chorea-acanthocytosis (CHAC)	Autosomal recessive	200150	Chorein (VPS13A) Homologue of *S. cereviciae* vacuolar protein sorting factor Vps13p (*VPS13A*)	Red cell acanthocytosis; basal ganglia atrophy in the brain; suggested defect in protein cycling between trans-Golgi network, endosomes and plasma membrane	Rampoldi et al., 2001; Ueno et al., 2001; Dobson-Stone et al., 2005; Velayos-Baeza et al., 2004; Brickner and Fuller, 1997
Chylomicron retention disease (CMRD) Anderson disease CMRD with Marinesco-Sjogren syndrome	Autosomal recessive	246700, 607689, 607692	Sar1b Small GTPase involved in vesicle budding from ER (*SARA2*)	Accumulation of chylomicron-like particles in membrane-bound compartments of enterocytes; large lipid droplets in enterocytes	Jones et al., 2003; Shoulders et al., 2004; Siddiqi et al., 2003; Siddiqi et al., 2006
Cohen syndrome	Autosomal recessive	216550	VPS13B Homologue of *S. cereviciae* vacuolar protein sorting factor Vps13p (*COH1*)	Marked phenotypic variability; cell biological consequences not extensively studied; multiple neurological defects; retinochoroidal dystrophy, neutropenia (not in all subjects)	Kolehmainen et al., 2003; Velayos-Baeza et al., 2004; Brickner and Fuller, 1997
Combined deficiency of coagulation factors V and VIII	Autosomal recessive	227300	ERGIC-53 ER-Golgi intermediate compartment sorter (*LMAN1*). MCFD2 Forms a complex with ERGIC-53 (*MCFD2*)	Defective secretion of coagulation factors V and VIII due to disturbed sorting to ER-Golgi carrier vesicles	Nichols et al., 1998; Zhang et al., 2003; Zhang et al., 2005; Zhang et al., 2006
Hermansky-Pudlak syndrome (HPS)	Autosomal recessive	203300	Type 2 Adaptor-related protein complex 3 beta-1 subunit (*AP3B1*). Types 1, 3-8 Components of the biogenesis of lysosome-related organelles complexes 1 to 3 (BLOC1 to BLOC3) (*DTNBP1* encodes dysbindin, *BLOC1S3*; *HPS3*, *HPS5*, *HPS6*; *HPS1*, *HPS4*)	Defective biogenesis of lysosome-related organelles (melanosomes, platelet dense granules, lamellar bodies of type II alveolar epithelial cells, T-lymphocyte lytic granules); leakage of lysosomal membrane proteins to cell surface	Wei, 2006; Gautam et al., 2006; Di Pietro and Dell'Angelica, 2005; Dell'Angelica et al., 1999; Peden et al., 2004; Robinson and Bonifacino, 2001; Boissy et al., 1998; Nazarian et al., 2003; Huizing et al., 2001; Huizing et al., 2004; Clark et al., 2003

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Table 1. Continued

Disease	Mode of inheritance	Online Mendelian inheritance in man (OMIM) number	Defective protein (gene)	Cellular phenotype	References
Category A					
Mucolipidosis II (I-cell disease) Mucolipidosis IIIA (classical pseudo-Hurler polydystrophy) Mucolipidosis IIIC (variant pseudo-Hurler polydystrophy)	Autosomal recessive	252500, 252600, 252605	N-acetylglucosamine-1-phosphotransferase Catalyses the formation of mannose 6-phosphate on lysosomal protein. α/β-subunits (*GNPTAB*), γ-subunit (*GNPTAG*)	Leakage of lysosomal hydrolases from cells due to lack of mannose-6-phosphate targeting signal; lysosomal accumulation of undegraded macromolecules	Tiede et al., 2005; Kudo et al., 2006; Raas-Rotschild et al., 2000; Raas-Rotschild et al., 2004
Lowe oculocerebrorenal syndrome	X-linked recessive	309000	OCRL1 PtdIns(4,5)P_2 5-phosphatase localized to the trans-Golgi network, early endosomes and clathrin-coated vesicles (*OCRL1*)	Secretion of lysosomal hydrolases; abnormalities of the actin cytoskeleton; accumulation of PtdIns(4,5)P_2; defective protein trafficking between trans-Golgi network and endosomes	Attree et al., 1992; Zhang et al., 1995; Suchy et al., 1995; Ungewickell et al., 2004; Choudhury et al., 2005; Halstead et al., 2005; Lowe, 2005; Hyvola et al., 2006
Periventricular heterotopia with microcephaly	Autosomal recessive	608097	ARFGEF2 (BIG2) Guanine nucleotide exchange factor forARF (*ARFGEF2*)	Defective neural precursor proliferation and neuron migration to cerebral cortex; myelination defect; experiments with cultured cells suggest function of ARFGEF2 in both ER-exit and post-Golgi vesicle transport	Sheen et al., 2004; Mouratou et al., 2005; Charych et al., 2004; Lu et al., 2006; Xu et al., 2005
Cranio-lenticulo-sutural dysplasia (CLSD)	Autosomal recessive	607812	SEC23A Component of the COPII coat that functions in membrane trafficking from the ER to the Golgi (*SEC23A*)	Abnormal bone and connective tissue formation – potentially resulting from a defect in the secretion of extracellular matrix proteins; dilatation of the ER in fibroblasts, cytoplasmic mislocalization of the COPII component SEC31	Boyadjiev et al., 2006; Lang et al., 2006; Barlowe et al., 1994; Antonny and Schekman, 2001; Bonifacino and Glick, 2004
Category B					
Amyotrophic lateral sclerosis 1 (ALS1)	Autosomal dominant	105400	p150^{glued} Subunit of dynein-dynactin, microtubule motor complex (*DCTN1*)	Progressive degeneration of motor neurons; disturbance of retrograde axonal transport	Munch et al., 2004; Munch et al., 2005; Kieran et al., 2005; LaMonte et al., 2002; Hafezparast et al., 2003
Charcot-Marie-Tooth disease, axonal, type 2B (CMT2B)	Autosomal dominant	600882	Rab7a Late endosomal small GTPase (*RAB7*)	Peripheral sensory neuropathy; axonal degeneration; experiments with cultured cells suggest function of Rab7 in trafficking of neutotrophin receptors – defects of which may lead to neurodegeneration	Verhoeven et al., 2003; Houlden et al., 2004; Saxena et al., 2005
Charcot-Marie-Tooth disease, axonal, type 2A1 (CMT2A1)	Autosomal dominant	118210	KIF1B Kinesin, microtubule motor (*KIF1B*)	Defects in sensory and motor-nerve functions; disturbed axonal transport of synaptic vesicle precursors	Zhao et al., 2001; Hirokawa and Takemura, 2003
Griscelli syndrome (GS)	Autosomal recessive	214450, 609227 256710	Types 1 and 3 Myosin 5a; an actin-based motor (*MYO5A*) Type 3 Melanophilin (Slac-2) bridges between myosin 5a and Rab27a Elejalde syndrome Suggested to represent the same entity as GS1	Accumulation of melanosomes in melanocytes, defect in melanosome tethering at peripheral actin (all three types); multiple neurological defects (type 1); uncontrolled T-lymphocyte and	Pastural et al., 1997; Ménasché et al., 2000; Ménasché et al., 2003; Fukuda et al., 2002; Anikster et al., 2002; Strom et al., 2002; Bahadoran et al., 2001; Stinchcombe et al., 2001; Wu et al., 1998; Wu et al.,

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Table 1. Continued

Disease	Mode of inheritance	Online Mendelian inheritance in man (OMIM) number	Defective protein (gene)	Cellular phenotype	References
Category B					
Griscelli syndrome (GS)	Autosomal recessive	607624	Type 2 Rab27a, small GTPase involved in regulated secretory processes (*RAB27A*)	macrophage activation; hemophagocytosis in multiple organs; defect in localizing secretory lysosomes to the immunological synapse in cytotoxic T cells (type 2)	2002; Libby et al., 2004; Barral et al., 2002
Huntington's disease	Autosomal dominant	143100	Huntingtin (Htt) Associates with microtubules and proteins involved in endo- or exocytic vesicle transport; antiapoptotic; involved in regulation of gene transcription; pathogenic forms contain expanded polyglutamine (polyQ) tracts (*HD*)	Accumulation of aggregated ubiquitin-conjugated proteins in neurons and glia; synapticdysfunction; selective neuronal death in cerebral cortex and striatum; polyQ-Htt disrupts microtubule association of dynactin and transport of brain-derived neurotrophic factor (BDNF); regulation of the transcription of neurotrophic factors by Htt may represent a major function related to the neurodegeneration	Harjes and Wanker, 2003; Smith et al., 2005; Valera et al., 2005; Gauthier et al., 2004; Humbert et al., 2002; Swayne et al., 2005; Kittler et al., 2004; Qin et al., 2004, Gunawardena et al., 2003; Zuccato et al., 2001; Zuccato et al., 2003
Lower motor neuron disease	Autosomal dominant	607641	$p150^{glued}$ Subunit of dynein-dynactin, microtubule motor complex (*DCTN1*)	Late-onset progressive degeneration of motor neurons; defects in retrograde axonal transport	Puls et al., 2003; Levy et al., 2006
Spastic paraplegia 4 (SPG4)	Autosomal dominant	182601	Spastin (AAA-type ATPase) Regulator of microtubule dynamics and endocytosis (*SPG4*)	Degeneration of the distal ends of long axons; defects in neuronal membrane trafficking suggested by the facts that spastin regulates microtubule stability to modulate synaptic structure and interacts with ESCRT-III complex	Hazan et al., 1999; Trotta et al., 2004; Evans et al., 2005; Reid et al., 2005; Salinas et al., 2005
Spastic paraplegia 10 (SPG10)	Autosomal dominant	604187	Kinesin 5A heavy chain, microtubule-based motor protein (*KIF5A*)	Degeneration of the distal ends of long axons; suggested defects in axonal membrane trafficking	Reid et al., 2002; Fichera et al., 2004; Blair et al., 2006; Lo Giudice et al., 2006
Category C					
Amyotrophic lateral sclerosis 8 (ALS8)	Autosomal dominant	608627	VAMP-associated protein B Implicated as SNARE regulator; localizes in ER and Golgi compartments; associates with microtubules; suggested function in the unfolded protein response (*VAPB*)	Progressive degeneration of motor neurons; possible disturbance of neuronal membrane trafficking; malfunction of VAPB to mediate unfolded protein response may contribute to motor neuron degeneration	Nishimura et al., 1999; Nishimura et al., 2004; Skehel et al., 2000; Hamamoto et al., 2005; Kanekura et al., 2006
Arthrogryposis-renal dysfunction-cholestasis (ARC syndrome)	Autosomal recessive	208085	VPS33B, a Sec1-Munc18-related (SM) protein Homologue of *S.c.* Vps33p involved in the biogenesis and function of vacuoles (*VPS33B*)	Suggested defects in membrane trafficking in the kidneys, liver, nervous system and platelets; defects in biogenesis of megakaryocyte and platelet α-granules; abnormal distribution of plasma membrane proteins; VAP33B overepression induces clustering of endo-lysosomes	Gissen et al., 2004; Gissen et al., 2005; Bull et al., 2006; Lo et al., 2005

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Table 1. Continued

Disease	Mode of inheritance	Online Mendelian inheritance in man (OMIM) number	Defective protein (gene)	Cellular phenotype	References
Category C					
Cerebral dysgenesis, neuropathy, ichtyosis, and palmoplantar keratoderma syndrome (CEDNIK syndrome)	Autosomal recessive	609528	SNAP-29 SNARE protein implicated as a general regulator of membrane trafficking; modulator of synaptic transmission (*SNAP29*)	Multiple neurological defects; progressive microcephaly; accumulation of abnormal vesicles in spinous and granular epidermal layers; abnormal maturation of lamellar granules; mislocation of epidermal glucosylceramides and proteases; suggested defect in vesicle transport	Sprecher et al., 2005; Su et al., 2001; Pan et al., 2005
Chediak-Higashi syndrome (CHS)	Autosomal recessive	214500	Lysosomal trafficking regulator (LYST, CHS1) Suggested to regulate lysosome size and docking/fusion at the plasma membrane (*CHS1*)	Giant melanosomes in melanocytes (hypopigmentation); enlarged lysosomes; Leakage of lysosomal or late endosomal proteins to early endosomes and cell surface; platelet dense granule deficiency; defective T- and NK-cell cytotoxicity and neutrophil bactericidal function; defective lysosomal exocytosis; progressive peripheral neuropathy	Barbosa et al., 1996; Spritz, 1998; Baetz et al., 1995; Nagle et al., 1996; Perou et al., 1997; Faigle et al., 1998; McVey Ward et al., 2002; McVey Ward et al., 2003; Huynh et al., 2004
Choroideremia (CHM)	X-linked recessive	303100	REP-1 (Rab escort protein 1) Factor required for the isoprenyl modification of Rab GTPases (*CHM*)	Degeneration of retinal pigment epithelium, choroid, and photoreceptor cells; defective isoprenyl modification of Rab GTPases	Cremers et al., 1990; Cremers et al., 1994; Merry et al., 1992; Seabra et al., 1992; Seabra et al., 1993; Seabra et al., 1995; Seabra et al., 2002; Rak et al., 2004
Danon disease	X-linked dominant	300257	Lamp2 (lysosome-associated membrane protein, *LAMP2*)	Major pathology in cardiac muscle; abundant intracytoplasmic autolysosomes (clusters of autophagic vacuoles) often surrounded by membranes with sarcolemmal proteins; glycogen accumulation in muscle	Nishino et al., 2000; Sugie et al., 2005; Eskelinen et al., 2003
Familial hemophagocytosis-lymphohistiocytosis (FHL)	Autosomal recessive	608898 603552	Type 3 hMunc13-4 Protein involved in transport vesicle/ secretory granule priming (*UNC13D*) Type 4 Syntaxin 11 SNARE protein localizing in late endosomes and trans-Golgi network (*STX11*)	Defect of T- and NK cells to release cytolytic granule contents; hemophagocytosis in bone marrow, cerebrospinal fluid or lymph nodes by activated histiocytes	Feldmann et al., 2003; zur Stadt et al., 2005; Shirakawa et al., 2004; Goishi et al., 2004; Neeft et al., 2005; Valdez et al., 1999
Spinal muscular atrophy (SMA), proximal, adult	Autosomal dominant	182980	VAMP-associated protein B Implicated as SNARE regulator, localizes in ER and Golgi compartments, associates with microtubules (*VAPB*)	Degeneration of spinal cord anterior horn cells; suggested dysfunction of vesicle transport	Nishimura et al., 1999, 2004; Skehel et al., 2000; Hamamoto et al., 2005

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Table 1. Continued

Disease	Mode of inheritance	Online Mendelian inheritance in man (OMIM) number	Defective protein (gene)	Cellular phenotype	References
Category C					
Tuberous sclerosis (TS)	Autosomal dominant	191100	Tuberin (Rab5GAP) GTPase-activating protein, modulator of endocytosis, tumor suppressor. Also shows GAP activity for the small GTPase Rap1 (*TSC2*)	Hamartomata in multiple organ systems; tumor formation; suggested defect in endocytic pathway function, leading to mis-sorting of internalized molecules that would normally undergo lysosomal degradation	Kumar et al., 1995; Xiao et al., 1997; Wienecke et al., 1995
X-linked non-specific mental retardation (MRX)	X-linked semidominant	309541	RabGDIα, Rab GDP dissociation inhibitor (*RABGDIA*)	Defective recycling and membrane targeting of Rab GTPases; possibly minor alterations in neuronal development	D'Adamo et al., 1998; D'Adamo et al., 2002; Bienvenu et al., 1998; Seabra and Wasmeier, 2004; Pfeffer and Aivazian, 2004
Spondyloepiphyseal dysplasia tarda (SEDT)	X-linked recessive	313400	Sedlin (homologue of *S. cerevisiae*; p20, Trs20p Component of the TRAPP complex that mediates tethering in ER-to-Golgi transport (*SEDL*)	Skeletal abnormalities and early-onset osteoarthritis; cell biological consequenses not well known; SEDL chondrocytes display excessive cytoplasm with abundant Golgi complexes and dilated rough ER	Gedeon et al., 1999; Gedeon et al., 2001; Tiller et al., 2001; Sacher et al., 1998; Sacher et al., 2001; Barrowman et al., 2000

by Rab GTPases (reviewed by Zerial and McBride, 2001; Whyte and Munro, 2002; Grosshans et al., 2006). Tethering progresses to more stable docking, after which fusion of the membrane bilayers occurs. Families of soluble N-ethylmaleimide sensitive factor attachment protein receptors (SNAREs) form the core of the machineries acting at this final stage of trafficking. SNAREs are present on vesicle and target membranes and form complexes thought to drive membrane fusion (reviewed by Rothman, 2002; Ungermann and Langosh, 2005; Jahn and Scheller, 2006). The function of SNAREs is controlled by a multitude of accessory factors, the number of which is exceptionally large in the synaptic vesicle and other Ca^{2+}-regulated fusion events (Gerst, 2003; Giraudo et al., 2006).

SNAREs and associated proteins

The first disease-causing mutations in SNARE proteins were discovered in 2005. A deletion in the gene encoding SNAP-29 was found to cause the neurocutaneous CEDNIK syndrome (Sprecher et al., 2005). Analysis of patient skin biopsies revealed abnormalities in the maturation of lamellar granules in the epidermis, as well as mislocation of epidermal glucosylceramide lipids and proteases, which contribute to the formation of the skin barrier and mediate desquamation, respectively. CEDNIK patients also display severe developmental abnormalities in the nervous system. SNAP-29 has been implicated as a generic SNARE protein that inhibits disassembly of SNARE complexes and modulates synaptic transmission (Su et al., 2001; Pan et al., 2005). The exact mechanisms through which the SNAP-29 defect induces the CEDNIK pathology are only partially understood, but the clinical findings, together with what we know about SNAP-29 from cell models, are consistent with a defect in membrane trafficking due to disturbance of the SNARE machinery.

The second SNARE defect identified, familial hemophagocytic lymphohistiocytosis (FHL), is caused by mutations in either syntaxin 11 (FHL type 4) (zur Stadt et al., 2005) or Munc13-4 (FHL type 3) (Feldmann et al., 2003), a Rab27a effector involved in mast cell degranulation (Neeft et al., 2005), secretion of cytolytic granules by CTLs (Feldmann et al., 2003), and secretion of dense core granules by platelets (Shirakawa et al., 2004). Although the functions of Rab27a and Munc13-4 can be linked in a relatively straightforward fashion to defects in cytolytic activity in FHL3 patients (see above), the mechanisms by which syntaxin 11 mutations result in the immunological symptoms in FHL4 are enigmatic. The function of syntaxin 11 has not been investigated in great detail. It colocalizes with MPR on late endosomes and the TGN, and is thought to regulate transport between these compartments (Valdez et al., 1999).

Mutations in a SNARE-interacting protein of the Sec1-Munc18 (SM) protein family, VPS33B, cause arthrogryposis-renal dysfunction-cholestasis (ARC) or incomplete ARC syndromes (Gissen et al., 2004; Bull et al., 2006). VPS33B is an orthologue of *Saccharomyces cerevisiae* Vps33p, which is involved in the biogenesis and function of the yeast vacuole (Peterson and Emr, 2001). However, the function of mammalian VPS33B has not been studied in detail. The cellular ARC phenotypes include abnormal distribution of plasma membrane proteins (Gissen et al., 2004) as well as platelet and megakaryocyte α-granule deficiency (Lo et al., 2005). Furthermore, VPS33B overexpression induces clustering of late endosomes/lysosomes (Gissen et al., 2004; Gissen et al., 2005), indicating that VPS33B is involved in late endosomal membrane dynamics. Together with the clinical features of ARC, these findings are consistent with abnormalities of vesicle transport in the kidney, liver, nervous

system and platelets being the underlying cause of ARC pathology.

Accessory factors for Rab GTPases

Genetic disorders caused by mutations in the factors that regulate Rab GTPases include choroideremia (CHM), tuberous sclerosis (TS), and X-linked non-specific mental retardation (MRX). The choroideremia defect has been pinpointed to Rab escort protein 1 (REP1) and was the first Rab-related defect discovered in a human disease (Cremers et al., 1990; Merry et al., 1992; Seabra et al., 1992; Seabra et al., 1993). REP1 acts as a cofactor in the geranyl-geranyl modification of cysteine residues in the C-terminal region of Rab GTPases, a process necessary for Rab membrane association. The CHM pathology results from degeneration of choroid and retinal photoreceptor cell layers (reviewed by Seabra et al., 2002). Even though REP1 represents a very fundamental part of the trafficking machinery, CHM cells retain the ability to process Rabs in a practically normal fashion owing to the presence of another REP isoform, REP2 (Cremers et al., 1994). This provides a plausible explanation for the limited nature of the CHM phenotype. Rab27 is prenylated more efficiently by REP1 than REP2 (Seabra et al., 1995) and expressed in the retinal cell layers that degenerate earliest in CHM; this suggests that Rab27 is the REP1 target critical for CHM pathology. However, the absence of pigmentation and immune system defects characteristic of GS2 patients suggests that the REP1 defect does not severely inhibit Rab27a function in all tissues. Notably, Rak et al. found that Rab27a has a relatively low affinity for both REP isoforms and thus competes poorly with other Rabs, which results in impaired prenylation under conditions in which the overall REP activity is low, such as in CHM (Rak et al., 2004).

The *TSC2* gene is mutated in a subset of patients with TS, a disease characterized by tissue hamartomata and tumors (Kumar et al., 1995). The protein, tuberin, is a GAP for the Ras relative Rap1 (Wienecke et al., 1995) and for Rab5, a regulator of early endocytic functions (Xiao et al., 1997). Cells lacking tuberin were reported to possess minimal Rab5 GAP activity and display enhanced fluid-phase endocytosis (Xiao et al., 1997). Tuberin defects may thus cause disturbances of endocytic pathway function and mis-sorting of internalized cargo that would normally be degraded in lysosomes. Such disturbances may be connected with the formation of intracellular inclusions and, eventually, hamartomata.

A further accessory factor for Rab GTPases, Rab GDP dissociation inhibitor α (RabGDIα), is defective in MRX (D'Adamo et al., 1998; Bienvenu et al., 1998). Deletion of the corresponding mouse gene, *Gdi1*, results in defective short-term memory, lowers aggression and alters social behavior. Thus, both in mouse and in humans, the defect spares most CNS functions and preferentially impairs only a few forebrain functions (D'Adamo et al., 2002). RabGDIα recycles GDP-bound Rabs via the cytosol and allows their specific re-insertion in the appropriate organelle membranes (reviewed by Seabra and Wasmeier, 2004; Pfeffer and Aivazian, 2004). As in CHM, inactivation of a central component of the trafficking machinery results in a relatively subtle and highly limited phenotype in MRX. In mammals, there are two RabGDI isoforms, and most of the functions of GDIα can obviously be executed by the second isoform, GDIβ. The mental retardation phenotype in MRX could result from minor disturbances in vesicle transport that lead to subtle abnormalities in CNS development.

Conclusions and future perspectives

Examination of these trafficking disorders reveals several recurrent themes. First, the nervous system is extremely sensitive to disturbances of the membrane trafficking machinery. Of the 30 diseases discussed here, neurological defects have been reported in 21. In the diseases that affect the movement of transport carriers along cytoskeletal tracks, all eight disorders covered represent neuropathies or involve major neurological symptoms. On one hand, this is predictable, because the nervous system is highly sensitive to various disturbances. This is illustrated by the fact that major pathology is neurological in most of the lysosomal storage diseases, even though lysosomal deposits occur in all tissues (reviewed by Sands and Davidson, 2006). On the other hand, the predominance of neurological symptoms reflects the highly active membrane transport functions of the nervous system. Generation and renewal of synaptic vesicles at the nerve termini require efficient and specialized membrane trafficking (reviewed by Südhof, 2004; Kavalali, 2006). The dimensions of neurites, especially the axon, set a requirement for efficient long-range transport via microtubules (Guzik and Goldstein, 2004; Hirokawa and Takemura, 2005). Furthermore, myelination necessitates efficient and specialized membrane trafficking in glial cells (Larocca and Rodriquez-Gabin, 2002).

Second, in several cases – such as CMRD, CLSD, choroideremia, MRX, and periventricular heterotopia with microcephaly – defects in a component that represents a fundamental part of the trafficking machinery fail to cause global transport defects but result in symptoms limited to specific cell types and transport events. This is most easily explained by the redundancy of the trafficking machinery: proteins related to those mutated can compensate for the defects in the majority of cells, and symptoms only arise when a given process is dependent on one specific isoform (e.g. because of strict substrate specificity or limits set by the expression level).

Third, in groups of closely related diseases such as HPS and GS syndromes, efforts to identify the underlying gene defects have revealed groups of gene mutations which lead to similar phenotypic consequences. New trafficking components that are functionally linked have thus been discovered. In the case of GS, disease gene identification has already revealed interactions between Rab27a, melanophilin and myosin 5a, and uncovered a major mechanism by which the subcellular distribution of melanosomes is regulated (Fig. 2A). In the case of HPS, the number of new proteins identified is exceptionally large (Fig. 1), and detailed elucidation of the functions of these components will, as for GS, greatly increase our understanding of the protein-protein interaction networks and molecular mechanisms operating in the biogenesis of lysosome-related organelles.

The ongoing study of the molecular mechanisms underlying the pathology of vesicle transport diseases employs modern gene identification approaches and bioinformatics, detailed phenotypic analysis of patients and cells derived from them, as well as animal models. This work is essential for bringing the molecular details of membrane trafficking into the larger

context of mammalian physiology and developmental biology. Furthermore, these efforts will in the future provide tools for developing novel therapeutic approaches. With improving gene transfer technologies, it will in some cases be possible to treat membrane trafficking diseases by providing the subject with a normal version of the mutated gene (Anand et al., 2003; Bizario et al., 2004). Furthermore, the developing stem cell therapy approaches provide good prospects for the treatment of neurological disorders, for instance (Lindvall and Kokaia, 2006). Detailed understanding of the molecular context in which the affected gene product functions should enable the development of intervention strategies based on bypassing the defective step. It may even be possible to apply a suppressor strategy in which manipulation of the activity of another gene product in the pathway compensates for the defect.

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