Mechanisms of Disease

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GENETIC DEFECTS OF INTRACELLULAR-MEMBRANE TRANSPORT

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THE compartmentalization of functions into distinct membrane-bound organelles is a central characteristic of cells. The protein and lipid composition of these organelles is unique, a factor that is vital for their proper function. This necessitates tightly controlled transport of biomolecules from their sites of synthesis or uptake to specific destinations, and mechanisms that prevent promiscuous interactions between cellular membranes that would lead to deleterious mixing of organelle constituents. One of the major processes responsible for the correct localization of molecules within the cell is called membrane or vesicular transport. In this process, membranous carrier structures bud off a donor compartment and fuse with a recipient one, thus delivering their membrane-associated and soluble luminal constituents to the target organelle.

Proteins to be transported within cells contain structural information that guides them to their correct destinations. Proteins with aberrant structures are misdirected and eventually degraded, as manifested in several inherited diseases in humans, such as cystic fibrosis and Marfan's syndrome.[1] During the 1990s, the cellular machinery responsible for decoding the targeting information on proteins and mediating the transport processes was described. Furthermore, several genetic diseases that directly affect the intracellular sorting and transport machinery were identified (Table 1). This review summarizes our current understanding of the membrane transport apparatus as well as the best-characterized examples of monogenic hereditary disorders caused by defects in this machinery. We used the following criteria to select the disorders covered in this review: the molecular defect has been pinpointed in a component with an established function in membrane transport, or the defect has been identified in a protein that is likely to be part of the vesicle-transport apparatus, and the cellular manifestations imply that there are disturbances in the function of the biosynthetic or endocytic transport pathways. The diseases thus chosen have been grouped into categories on the basis of the presumed function of the defective gene product. Consequently, the selected defects display certain unifying features from which we may better understand the principles underlying the complex processes of cellular transport and their role in human disease.

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INTRACELLULAR-MEMBRANE TRANSPORT

The major cellular routes of membrane transport are the biosynthetic pathway responsible for the transport of proteins synthesized in the endoplasmic reticulum to the extracellular space (secretion) or to other cellular-membrane compartments and the endocytic pathway responsible for the uptake of compounds from the extracellular milieu to be used in cellular metabolism (Fig. 1). 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 the glycosylation of proteins. Proteins that are destined to be transported out of the endoplasmic reticulum move on to the Golgi apparatus, where further post-translational modifications occur. Subsequently, the proteins are sorted according to their destinations: the plasma membrane (e.g., ion channels, adhesion molecules, and various receptors), regulated secretory granules or vesicles (e.g., hormones, enzymes, and neurotransmitters), or organelles of the endocytic pathway (e.g., lysosomal hydrolases).[8,9]

Extensive sorting of internalized molecules also takes place along the endocytic pathway: selected molecules are returned to the surface of the cell (e.g., recycling receptors), whereas others are transported to late endosomes and lysosomes, where they are internalized and then degraded. The outgoing and incoming pathways communicate through the exchange of material between the Golgi apparatus and the endosomal elements.[10,11] 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. These stages include the sorting of proteins and lipids, the formation of transport vesicles, movement of the vesicles along cytoskeletal filaments, recognition of the target organelle, and fusion of the vesicles with the acceptor compartment (Fig. 2). In the past few years the use of novel techniques to follow transport intermediates in living cells has revealed that, in vivo, the carriers not only are spherical but also in many cases form long tubular projections in the cell.[12]

SORTING OF PROTEINS TO TRANSPORT VESICLES

The first step in transport involves the selection of passengers. There is increasing evidence that proteins

TABLE 1. GENETIC DISORDERS OF INTRACELLULAR-MEMBRANE TRANSPORT.

DISORDER	MODE OF INHERITANCE	MUTANT PROTEIN	CELLULAR DEFECT	MOUSE MODEL
Inclusion-cell disease, also called mucolipidosis II	Autosomal recessive	*N*-acetylglucosamine-1-phosphotransferase	Leakage of lysosomal hydrolases from cells owing to the lack of the mannose-6-phosphate targeting signal; lysosomal accumulation of undegraded macromolecules	None
Combined deficiency of coagulation factors V and VIII	Autosomal recessive	ERGIC-53, a mannose-binding lectin that cycles between the endoplasmic reticulum and Golgi apparatus	Defective secretion of coagulation factors V and VIII; disturbed sorting to transport vesicles in the endoplastic reticulum	None
Hermansky–Pudlak syndrome	Autosomal recessive	AP-3 adaptor complex β3A subunit or HPS1	Defective genesis of lysosomes or related organelles, leakage of lysosomal-membrane proteins to the cell surface	Pearl[2]
Chédiak–Higashi syndrome	Autosomal recessive	Lysosomal-trafficking regulator	Enlarged lysosomes, leakage of lysosomal or late endosomal proteins to early endosomes and the cell surface; defective cytotoxicity of T cells and natural killer cells; deficiency of neutrophil-mediated bactericidal activity	Beige[3]
Oculocerebrorenal syndrome	X-linked	OCRL-1, an inositol polyphosphate 5-phosphatase	Secretion of lysosomal hydrolases; accumulation of phosphatidylinositol 4,5-bisphosphate	*OCRL1*-knockout mice[4]
Griscelli's syndrome	Autosomal recessive	Myosin-Va	Reminiscent of that in the Chédiak–Higashi syndrome	Dilute[5]
Usher's syndrome type 1B	Autosomal recessive	Myosin-VIIa	Degeneration of retinal and cochlear sensory cells	Shaker-1[6]
Choroideremia	X-linked	Rab escort protein 1	Degeneration of retinal pigment epithelium, choroid, and photoreceptor cells; defective lipid modification of Rab guanosine triphosphatases	*REP/1*-knockout mice[7]
X-linked nonspecific mental retardation	X-linked	Rab GDP-dissociation inhibitor	Defective recycling and membrane targeting of Rab guanosine triphosphatases; may cause minor alterations in neuronal development	None

destined for transport and the vesicle-targeting machinery are actively recruited to specific sites on the limiting membrane of the organelle where transport intermediates bud off. This process takes place with the aid of cytosolic complexes of coat protein that directly interact with transmembrane proteins or receptors for luminal molecules (Fig. 3).[13-15] Along with proteinaceous regulatory factors, the lipid composition of the membranes has an important role in the recruitment of coat proteins and the budding of transport vesicles.[16] The inclusion of proteins in transport intermediates involves the interpretation of hierarchical sorting signals in the molecules to be transported. These represent biochemically different recognition principles, including specific amino acid determinants, saturated fatty acyl moieties, and carbohydrates that can be recognized by lectin-like receptors.[17,18] Furthermore, dynamic lipid domains formed by cholesterol and glycosphingolipids are instrumental in the sorting of certain membrane-associated proteins.[19] Together, these different processes generate an extensive integrated network of sorting events, the outcome of which is a fine-tuned dynamic equilibrium in the distribution of cellular constituents.

CYTOSKELETAL TRACKS FOR THE MOVEMENT OF VESICLES

Once a vesicle has budded off, it does not move passively but rather is guided toward the target membrane by the filamentous structures of the cytoskeleton. Proteins that use the energy of ATP to propel the movement of vesicles or organelles along these filaments are called cytoskeletal motor proteins (Fig. 2). In mammalian cells, microtubules and the associated kinesin and dynein motor proteins form the principal apparatus responsible for organizing directional membrane flow. In addition, elements consisting of actin and spectrin are thought to connect transport vesicles to microtubules.[20] Furthermore, actin microfilaments, together with myosin motor proteins,[21] form tracks for the short-distance movement of vesicles, such as when a secretory vesicle has been delivered to the cortical region of the cell and is approaching the plasma membrane.

FUSION OF TRANSPORT VESICLES WITH TARGET MEMBRANES

The apparatus responsible for the mutual recognition of a transport vesicle and its target membrane

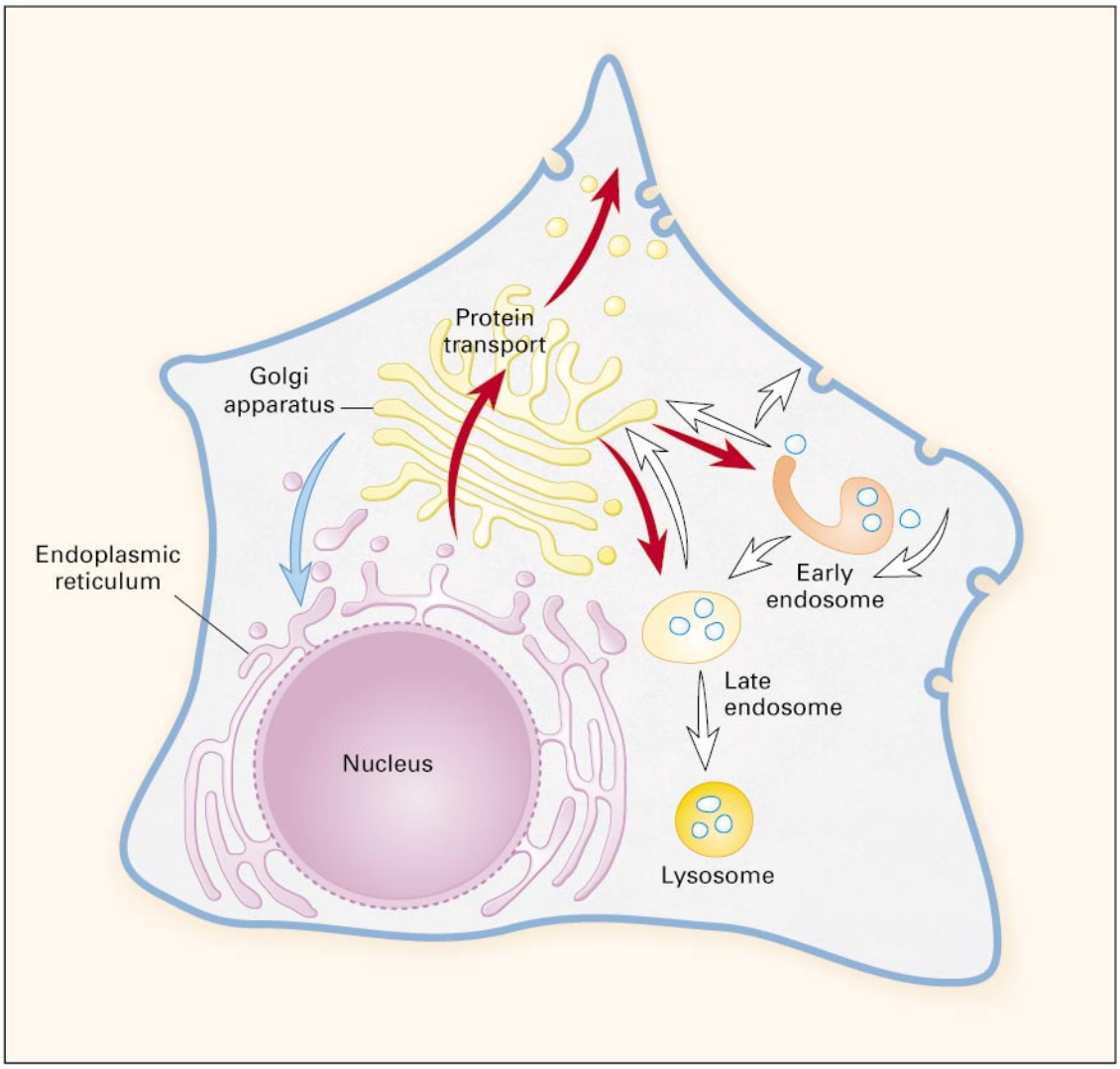

Figure 1. Pathways of Intracellular-Membrane Transport.

The biosynthetic pathway (indicated by red arrows) transports proteins from the endoplasmic reticulum through the Golgi complex to the cell surface. Molecules internalized from the external milieu (indicated by white arrows) reach the early endosomes and can then be either recycled back to the surface or transported to late endosomes and lysosomes. Retrograde transport through the biosynthetic pathway is indicated by the blue arrow. The biosynthetic and endocytic circuits exchange material at the level of the Golgi apparatus and the endosomal elements.

(tethering and docking) and the subsequent bilayer fusion have been studied intensively during the past decade. The initial interaction between vesicles and their target membrane is facilitated by the regulated assembly of oligomeric protein complexes linking the two membranes together.[22] Although the molecular events taking place during bilayer fusion are not known in detail, highly conserved membrane-anchored proteins are believed to be instrumental.[23] The mutual recognition of a transport vesicle and its target organelle is controlled by cycles of nucleotide binding and hydrolysis by Rab proteins, small guanosine triphosphatases (GTPases) belonging to the Ras superfamily.[24,25] The GTPase cycle and the attachment of Rab proteins to the membrane are in turn modulated by accessory protein factors (Fig. 4).

INHERITED DISEASES CHARACTERIZED BY DEFECTS IN INTRACELLULAR PROTEIN TRANSPORT

Defects Affecting the Protein-Sorting Apparatus

Inclusion-cell disease, also called mucolipidosis II, is the prototypical genetic disorder affecting the machinery of protein sorting. This syndrome is characterized

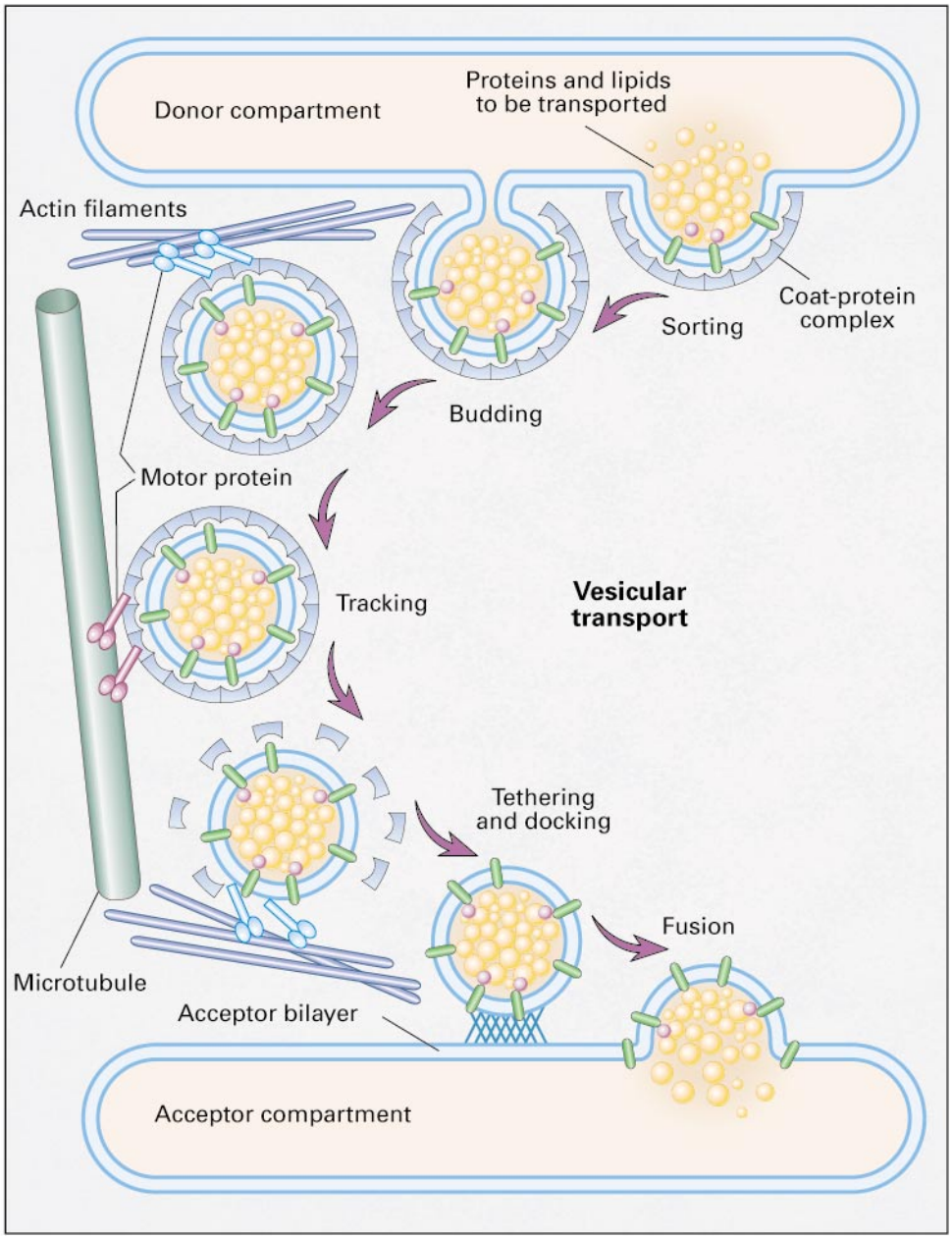

Figure 2. Vesicular Transport.

Proteins and lipids to be transported are sorted to specific sites on the donor membrane, or compartment, and transport vesicles bud with the aid of cytosolic complexes of coat proteins. Vesicles move along cytoskeletal tracks, either microtubules or actin filaments, with the help of motor proteins. The vesicle is tethered and docked near the target membrane and subsequently fuses with the acceptor bilayer, releasing its contents into the target, or acceptor, compartment.

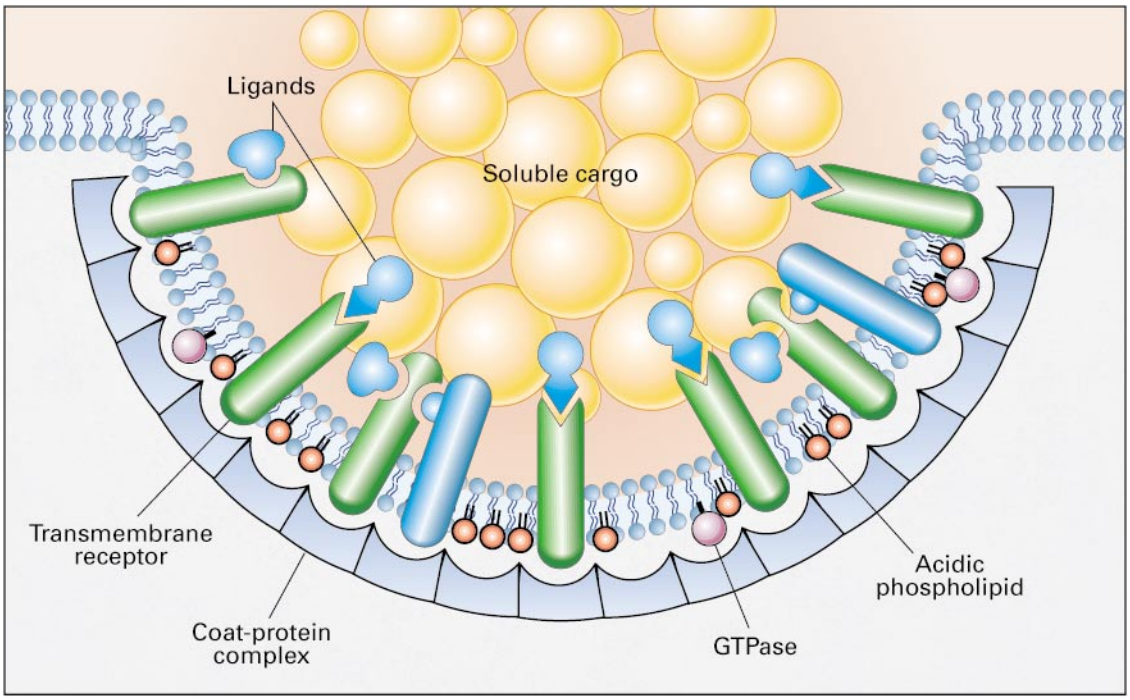

Figure 3. Sorting of Proteins to Transport Vesicles at the Donor Membrane.

Transmembrane receptors that bind soluble and membrane-bound ligands can interact with cytosolic complexes of coat protein. Small guanosine triphosphatases (GTPases) anchored to the cytosolic face of the donor membrane are critical for the assembly of the coat-protein complex. The lipid composition of the membrane (e.g., the content of acidic phospholipids) also has an important role in the formation of vesicles. Examples of genetic defects that affect the sorting of proteins to vesicles include inclusion-cell disease (caused by a defective mannose-6-phosphate recognition marker on ligands), combined deficiency of coagulation factors V and VIII (caused by a defective transmembrane lectin-type receptor), and the Hermansky–Pudlak syndrome (caused by a defective subunit of a coat-protein complex).

by the leakage of multiple lysosomal hydrolases from cells, which leads to abnormally low cellular concentrations of these enzymes and to the lysosomal accumulation of undegraded macromolecules.[26] The major clinical consequences include multiple skeletal abnormalities (e.g., congenital hip dislocation and dwarfism), hepatosplenomegaly, and retarded psychomotor development. The lysosomal deposits probably interfere with cellular physiology in multiple organ systems through direct toxic effects or by mechanical disturbance. The molecular defect of inclusion-cell disease was recognized as a lack of the mannose-6-phosphate modification of the glycans present on the lysosomal hydrolases. This modification functions as a recognition tag for the mannose-6-phosphate receptors that capture lysosomal enzymes from the Golgi apparatus and the cell surface and direct them to vesicles destined for transport to endosomes and lysosomes (Fig. 3).[27,28] In patients with inclusion-cell disease, the activity of the Golgi enzyme *N*-acetylglucosamine-1-phosphotransferase, one of the two enzymes responsible for synthesizing the mannose-6-phosphate tag, is missing. A related defect with milder symptoms, pseudo-Hurler polydystrophy, is caused by a less drastic impairment in the activity of the same glycan-modifying enzyme.

The defect in inclusion-cell disease affects the ligand to be sorted, whereas mutations in a sorting receptor that recognizes carbohydrate ligands were recently characterized as the cause of a bleeding syndrome: the combined deficiency of coagulation factors V and VIII. This clinical entity, which is characterized by a moderate bleeding tendency and low plasma concentrations of these two factors, is caused by mutations in ERGIC-53, a mannose-binding lectin that cycles between the endoplasmic reticulum and the Golgi apparatus.[29] ERGIC-53 may interact with coat-protein complexes that drive the budding of transport vesicles in the early secretory pathway and may thus be directly involved in the sorting of glycoproteins (Fig. 3).[30,31] The ERGIC-53 protein was totally absent in cells of patients who were homozygous for the mutation, leading to defective secretion of the two coagulation factors, which were apparently re-

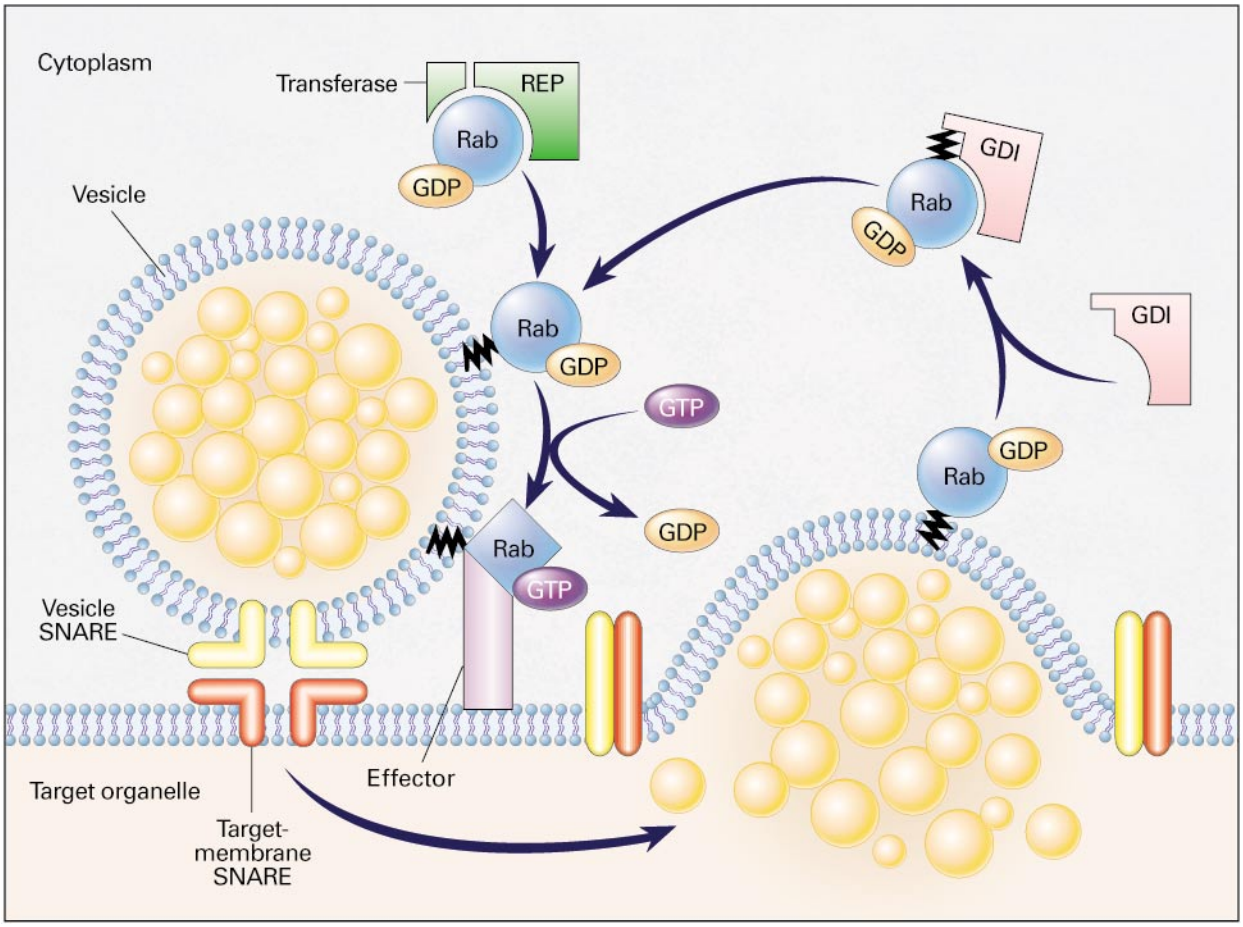

Figure 4. Targeting and Fusion of Vesicles with the Target Organelle.

The Rab proteins are key regulators of the tethering and fusion of vesicles. They cycle between forms bound by guanosine triphosphate (GTP) and guanosine diphosphate (GDP) and shift between cellular membranes and the cytoplasm with the help of the Rab GDP-dissociation inhibitor (GDI). The membrane association of Rab proteins is dependent on hydrophobic modification mediated by Rab escort protein (REP) and an isoprenyl transferase. The function of Rab guanosine triphosphatases (GTPases) and their effectors is apparently linked to that of the highly conserved membrane-anchored proteins (SNAREs) acting farther downstream in the vesicle fusion process. The pairing of these proteins on the vesicle and target membranes is needed for bilayer fusion. Examples of genetic defects that affect the function of Rab proteins include choroideremia, in which Rab escort protein 1 is defective, and X-linked mental retardation, in which the Rab GDP-dissociation inhibitor is defective.

tained in the endoplasmic reticulum. However, the patients had normal plasma concentrations of other proteins, suggesting that the function of ERGIC-53 is specific for a subgroup of the glycoproteins that are transported out of the endoplasmic reticulum.

The first inherited defect in the coat-protein complexes in the vesicle was identified in patients with the Hermansky–Pudlak syndrome. This syndrome is characterized by oculocutaneous albinism, bleeding diathesis, and storage of abnormal ceroid-like material in cells of the reticuloendothelial system.[32] Pulmonary fibrosis or granulomatous colitis develops in some patients, probably because of the accumulation of undegraded macromolecules in the lysosomes of reticuloendothelial cells. The common denominator is deficient genesis or abnormal function of lysosomes or related cellular organelles: a disturbance in the maturation of melanosomes results in hypopigmentation, whereas a deficiency of platelet dense granules causes a chronic bleeding problem owing to defective secretion of compounds essential for activation of platelets. A gene of unknown function called *HPS1* was found to be mutated in some patients with the Hermansky–Pudlak syndrome,[33] whereas in a subgroup of patients the cause has been found to lie in a gene encoding a subunit of the AP-3 coat-protein complex.[34] Fibroblasts from the patients displayed drastically reduced concentrations of AP-3 and, as a consequence, in-

creased surface expression of several lysosomal-membrane proteins. These findings provide insight into the function of the AP-3 complex and are evidence that AP-3 has a role in the transport of transmembrane proteins destined for the lysosomes.

Another sorting disorder characterized by abnormalities of pigmentation and blood clotting is the Chédiak–Higashi syndrome.[35] Affected patients also have neurologic dysfunction and various immunologic deficits leading to life-threatening pyogenic infections. The cellular hallmarks of the Chédiak–Higashi syndrome include large lysosomal granules in leukocytes, giant melanosomes in melanocytes, a deficiency of neutrophil-mediated bactericidal activity, and loss of cytotoxicity of T cells and natural killer cells. The giant melanosomes fail to mature normally and are subject to premature destruction through fusion with lysosomes, leading to pigmentary dilution and oculocutaneous albinism. The loss of T-cell cytotoxicity is apparently due to the cells' inability to secrete cytolytic proteins stored in the giant granules.[36] The Chédiak–Higashi syndrome is caused by mutations in a gene encoding a cytosolic protein named lysosomal-trafficking regulator.[3,37,38] The structure of this protein is similar to that of a well-characterized protein involved in vacuolar sorting in budding yeast, a model corresponding to lysosomal-protein transport in mammals. This finding, together with the abnormal distribution of late endosomal or lysosomal proteins in cells from patients with the Chédiak–Higashi syndrome,[39] is consistent with the idea that a primary defect in molecular sorting occurs in the Golgi apparatus or endosomes.

Defects in Cytoskeletal Proteins Involved in Membrane Transport

Griscelli's syndrome, whose clinical manifestations are similar to those of the Chédiak–Higashi syndrome,[40] is caused by mutations in a gene encoding the unconventional myosin termed myosin-Va.[41] Unconventional myosins of several classes have been implicated as cytoskeletal proteins involved in actin-dependent movement of organelles and membrane transport in a variety of organisms (Fig. 2).[21] Studies of mice lacking myosin-Va have indicated that it is involved in distributing melanosomes to the cell periphery[42] and in the local movement or processing of organelles in specific regions of neurites.[43] This finding sheds light on the cause of the pigmentary dilution and the neurologic symptoms associated with the disease in humans. The similarity of the phenotypes of Griscelli's syndrome and the Chédiak–Higashi syndrome indicates that the products of the genes encoding myosin-Va and lysosomal-trafficking regulator may interact physically or function in the same intracellular transport pathways responsible for the normal dynamics of lysosome-related organelles.

Specific myosins are implicated in sensory transduction. Mutations in the genes encoding myosin-VI and myosin-VIIa have been linked to several disorders characterized by deafness in humans.[21] The strongest evidence of a defect in vesicular transport in this group of diseases is found in Usher's syndrome type 1B, which is caused by mutations in the gene for myosin-VIIa.[44] In addition to deafness, patients with this syndrome have retinitis pigmentosa, which leads to blindness. Myosin-VIIa is abundant in the synaptic regions of photoreceptor cells and presumably acts as an actin-based motor protein involved in the formation and transport of the ribbon–synaptic vesicle complexes characteristic of these sensory cells. Furthermore, myosin-VIIa may be involved in the renewal of the outer photoreceptor disks, a process requiring efficient membrane transport,[45,46] and in endocytic transport in cochlear hair cells.[47]

Defects in the Machinery for the Docking and Fusion of Transport Vesicles

Despite the fact that the protein machinery involved in the docking and fusion of transport vesicles has been characterized extensively in the past 10 years, there are only two diseases in humans in which the genetic defect has been traced to this highly conserved machinery. Both these diseases — choroideremia and X-linked nonspecific mental retardation — involve mutations in the auxiliary protein factors controlling the membrane association of the Rab GTPases (Fig. 4). Choroideremia is an X-linked form of retinitis pigmentosa characterized by degeneration of the retinal pigment epithelium and the adjacent choroid and retinal photoreceptor-cell layers. The gene mutated in choroideremia was identified as that encoding component A of the Rab geranylgeranyltransferase, also designated Rab escort protein 1 (REP-1).[48-51] This protein and its isoform, Rab escort protein 2 (REP-2),[52] are essential for the modification of the Rab GTPases by hydrophobic isoprenoid moieties that mediate their membrane association.[24] Why does a defect in a widely expressed gene encoding a central component of the transport machinery have such a limited phenotype? The answer probably lies in the overlapping patterns of expression and substrate specificities of the isoforms of the Rab escort protein; REP-2 is most likely capable of compensating for the loss of activity of REP-1 in most tissues. However, the small GTPase Rab27 that is expressed in the retinal-cell layers subject to degeneration in choroideremia preferentially interacts with the REP-1 isoform.[53] Therefore, disturbed function of Rab27 may lead to a specific membrane-transport abnormality in the affected retinal cells.

The genetic background of X-linked nonspecific mental retardation is heterogeneous, with at least 8 to 10 loci thought to be involved in different families. In a subgroup of families with this disorder, the genetic defect is in the gene encoding the Rab guano-

sine diphosphate (GDP)–dissociation inhibitor α,[54] a protein that controls the intracellular recycling of Rab GTPases.[55] These proteins can bind GDP-bound Rab proteins and deliver them in a controlled manner to specific organelles. This situation resembles that in choroideremia, in that the GDP-dissociation inhibitors constitute a family of protein isoforms, of which the isoform α is predominantly expressed in the central nervous system. Mutant GDP-dissociation inhibitor may not be able to recycle Rab proteins efficiently in vivo.[54] Thus, mutations in GDP-dissociation inhibitors may ultimately alter synaptic transmission. Furthermore, studies in mice suggest that GDP-dissociation inhibitor α has a role in neuronal differentiation. The surprisingly mild phenotypic effects of mutations of GDP-dissociation inhibitor α are probably due to the presence of other, "housekeeping" isoforms of these proteins in neurons.

Lipid Disorders Affecting Vesicular Transport

The oculocerebrorenal syndrome is characterized by failure to thrive and the triad of renal tubular acidosis, congenital cataracts, and mental retardation. The renal dysfunction is characterized by bicarbonate wasting, aminoaciduria, phosphaturia, and proteinuria coupled with a defect in urinary concentration. Furthermore, the cells secrete abnormally large amounts of lysosomal hydrolases. The gene mutated in the syndrome encodes a protein, OCRL-1,[56] an inositol polyphosphate 5-phosphatase that catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate to phosphatidylinositol 4-phosphate.[57,58] The clinical findings suggest that the OCRL-1 protein regulates the transport of lysosomal hydrolases and other proteins by controlling the concentrations of phosphatidylinositol 4,5-bisphosphate in lysosomal or Golgi membranes. The severity of the symptoms underscores the recently uncovered central role of polyphosphoinositide lipids in membrane transport.[59]

Connections between cholesterol transport and intracellular-membrane transport are emerging.[60] The study of Niemann–Pick disease type C provides interesting clues to the role of membrane cholesterol and membrane domains enriched with cholesterol and glycosphingolipids in vesicular transport and membrane-associated sorting events. Niemann–Pick disease type C is characterized by the storage of lipids in various tissues, the clinical hallmark being severe neurodegeneration. In the cells of patients with this disorder, free cholesterol is unable to exit lysosomes because of mutations in a gene that encodes NPC-1, a multimembrane-spanning protein found in late endocytic compartments.[61-63] The lysosomal accumulation of cholesterol and the resulting disturbance of cellular cholesterol homeostatic responses are likely to disrupt the organization of lipid microdomains in cellular membranes. This effect may account for some of the observed disturbances in protein localization in affected patients[64,65] and may constitute part of the molecular background of the neurodegenerative symptoms.

CONCLUSIONS

On the one hand, elucidation of the machinery of intracellular-membrane transport and the development of powerful techniques for the identification of disease-causing genes on the other are providing us with new information on the way in which disturbances in the intracellular transport of proteins and lipids cause disease in humans. All the molecular defects that we have discussed were identified in the 1990s, and the progress in the field is likely to accelerate. However, elucidating in detail the pathway from a specific mutation to the disease symptoms will be a more laborious and time-consuming task. The strains of mutant or gene-knockout mice available for several of the disorders (Table 1) will facilitate this process. They will also provide models for testing new therapeutic approaches.

The theoretically attractive idea of providing affected patients with a normal version of the mutated gene is often not feasible. Knowing the molecular context in which the affected gene product functions can allow us to develop intervention strategies based on bypassing the defective step. It may even be possible to apply a suppressor type of strategy, used widely in lower eukaryotes, in which manipulation of the activity of other gene products in the pathway may compensate for the defect.

An intriguing feature of the group of diseases summarized here is that defects that affect components of the same molecular apparatus can manifest themselves in many different ways. On the other hand, similar phenotypic effects may result from mutations in very different types of gene products. It is evident that it will be difficult, if not impossible, to predict the location of a molecular defect in the intracellular-transport machinery on the basis of clinical findings alone. One of the main reasons for this is probably the redundancy of the machineries responsible for membrane transport. This point is well illustrated by choroideremia and X-linked nonspecific mental retardation: mutations in REP-1 and GDP-dissociation inhibitor α cause highly specific and limited phenotypes, obviously because of the ability of related gene products to compensate for the defects in a majority of cells. It is also noteworthy that functional redundancy within the membrane transport system sometimes leads to surprising results in animal models: for example, inactivation of the *OCRL1* gene in mice failed to reproduce the abnormalities that occur in humans with the oculocerebrorenal syndrome, indicating that in mice, another gene product compensates for the loss of the OCRL-1 protein.[4]

In some transport diseases, such as the Hermansky–Pudlak syndrome and X-linked nonspecific mental retardation, the genetic background is remarkably het-

erogeneous. Identification of novel genes in these groups of diseases is likely to reveal new components of the machineries or pathways in which the known proteins act. Furthermore, it can be anticipated that genetic polymorphisms in the components of the intracellular-membrane transport apparatus will turn out to be involved in the polygenic background of common diseases. For instance, susceptibility to atherosclerosis may in some cases be linked to variations in the gene found recently to be defective in patients with Tangier disease and familial high-density lipoprotein deficiency.[66] This gene product, ATP-binding cassette transporter A1, facilitates the mobilization of cellular cholesterol to plasma lipoproteins.[67] An important determinant of the process of cholesterol efflux is the movement of cholesterol from intracellular stores to the plasma membrane, which may involve the membrane-transport apparatus.[68,69]

Another example of the relevance of the membrane-transport paradigm is the uptake of glucose by muscle and adipose tissue. This process depends on the localization of GLUT-4 glucose transporter on the surface of cells. GLUT-4 molecules reside in intracellular stores and, on stimulation by insulin, are translocated to the plasma membrane through fusion of the storage vesicles.[70] There is a precedent for defective transport and translocation of GLUT-4 as a cause of insulin resistance,[71] implying that elucidation of the mechanisms of glucose-transporter transport may reveal new candidate genes involved in type 2 diabetes mellitus.

Furthermore, dysfunctions of vesicular-transport mechanisms are not restricted to genetic disorders: several microbial pathogens are capable of escaping immune surveillance by interfering with host-cell antigen presentation. This can be accomplished by disturbing the intracellular sorting of multiple histocompatibility complex proteins, which then become unable to reach the surface of the cell.[72] These examples serve to illustrate how the concepts of intracellular-membrane transport will help not only to elucidate the pathology of rare single-gene disorders but also to dissect the molecular causes of more common diseases in humans.

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