Molecular Mechanisms of Organelle Biogenesis and Related Metabolic Diseases

Gursev S. Dhaunsi

Department of Pediatrics, Faculty of Medicine, Kuwait University, Kuwait

Key Words

Organelle biogenesis · Mitochondria · Lysosomes · Peroxisomes · Metabolic diseases

Abstract

Organelle biogenesis is regulated by transcriptional networks that modulate expression of specific genes encoding organellar proteins. Structural and functional specificity of organelles requires not only the transcription of specific genes and translation of resulting mRNAs, but also the transfer of encoded polypeptides to their site of function through signaling peptides. A defect in targeting of proteins to their subcellular site of function may not necessarily prevent biogenesis of the organelle, but would definitely lead to formation of a defective organelle with respect to that specific function. Several metabolic diseases are associated with dysfunction or defects in organelle biogenesis; among these, peroxisome biogenesis disorders, mitochondrial biogenesis defects and lysosomal storage disorders are an extensively studied group of genetic diseases where biogenesis of the organelle is compromised either due to a defect in assembly of the organelle itself or impaired import of matrix proteins into the organelle. Recent advances in biochemical and molecular aspects of biogenesis of subcellular organelles have not only unraveled the mechanisms for organization of cellular networks, but have also provided new insights into the development of metabolic diseases that are caused by disruption of organelle biogenesis.

This article reviews the molecular mechanisms of biogenesis of mitochondria, lysosomes and peroxisomes in relation to the metabolic diseases of genetic or nongenetic origin.

Copyright © 2005 S. Karger AG, Basel

Introduction

Complex organization of distinct membrane-bound compartments, called subcellular organelles, in eukaryotic cells forms the cellular basis of human physiology. Subcellular organelles interact with each other through their highly specialized metabolic activities and sustain various cellular functions. The amount, size and composition of each organelle in a cell are determined by the cellular metabolic needs according to its environment in the body. A complete set of organelles such as nucleus, mitochondria, endoplasmic reticulum, peroxisomes and lysosomes are always inherited maternally and proliferation, also termed organelle biogenesis, of these endowed organelles leads to an increased number and size of specialized membrane-bound cell compartments [1, 2].

Organelle biogenesis is regulated by transcriptional networks that modulate expression of specific genes encoding organellar proteins. Structural and functional specificity of organelles requires not only the transcription of specific genes and translation of resulting mRNAs, but also the transfer of encoded polypeptides to their site of function [3]. Proteins required for biogenesis of all sub-

cellular organelles are encoded by nuclear genes except for mitochondria, where expression of both nuclear and mitochondrial genes is required for normal structure and metabolic functions of mitochondria [4, 5].

Several metabolic diseases are associated with dysfunction of organelle biogenesis and among these human diseases, there are three well-defined groups of deadly genetic disorders, namely mitochondrial disorders, lysosomal diseases and peroxisomal disorders, where functions of membrane-bound intracellular organelles are impaired [6–9]. Significant advances in biochemical and molecular aspects of biogenesis of subcellular organelles have been made which have unraveled the role of specific transcription factors in the expression of mitochondrial, lysosomal and peroxisomal proteins. Studies revealing the selective translocation of organellar proteins into the organelles through specific targeting signals have further clarified the complex process of organelle biogenesis [10, 11]. These recent developments in cell biology have not only unraveled the mechanisms for organization of cellular networks, but have also provided new insights into the development of metabolic diseases that are caused by disruption of organelle biogenesis.

Functions of various subcellular organelles are compromised not only in genetic disorders of organelle biogenesis, but several metabolic disturbances also occur during diseases of nongenetic origin such as infections, intoxications and drug treatments. Better understanding of biochemical and molecular aspects of organelle biogenesis strengthens the hope for correcting or preventing the impairment of metabolic activities during various pathological conditions of both genetic and nongenetic origin. This article aims to give an overview of our current knowledge about molecular mechanisms of biogenesis of mitochondria, lysosomes and peroxisomes, and inherited disorders in which these organelles are lacking or their functions are impaired due a defect in biogenesis.

Mitochondrial Biogenesis and Relevant Diseases

The mitochondria are the powerhouse of eukaryotic cells where aerobic ATP production during coupled oxidative phosphorylation is the key function along with numerous other biosynthetic and degradative reactions fundamental to cell function [12]. Recent advances in molecular cell biology have revealed that mitochondria also play a role in regulating the cellular life cycle through the release of cytochrome c, an important stimulator of apop-

toxis [13, 14]. The distinctive mitochondrial structure, which allows specialized functions involving different enzymes and reactions localized in discrete membranes and aqueous compartments, is the product of both synthesis of macromolecules within the mitochondria and the import of proteins and lipids synthesized outside the organelle. Mitochondria are maternally inherited and their growth is facilitated by synthesis and import of new mitochondrial components. Although the mitochondrion contains its own genetic material, the majority of its protein is derived from the nucleus, including the proteins involved in mitochondrial transcription and DNA replication. Distinct from the nuclear DNA, mammalian mitochondrial DNA (mtDNA) is a small circular molecule consisting of 16–18 kb that only encodes 13 mRNAs, 22 tRNAs and 2 rRNAs, of which all protein products function in the respiratory chain of the inner mitochondrial membrane. The nuclear genes for proteins to be targeted to the mitochondria are transcribed in the nucleus, translated in the cytosol, and translocated into the mitochondria, and this process of mitochondria biogenesis is regulated in a complex way through activation of specific transcription factors. Mitochondrial transcription factor A (Tfam) plays an important role in mtDNA transcription and replication [15, 16], and an increase in Tfam expression would precede alterations in mitochondrial gene expression. The promoter region of the human TFAM gene has a binding site for nuclear respiratory factor (NRF) that appears to be crucial in regulating the transcriptional activation of this gene [17]. The NRFs (NRF-1 and NRF-2) have been identified as nuclear transcription factors, and are common to a large number of nuclear-encoded mitochondrial proteins [18]. NRF-1 appears to bind to DNA as a homodimer where its C-terminal end activates transcription, while phosphorylation of NRF-1 on N-terminal serine residues enhances its DNA binding ability [19, 20]. In addition to its role in regulating Tfam expression, NRF-1 may furthermore influence mtDNA maintenance through its activation of the RNase mitochondrial RNA processing endonuclease. The RNase mitochondrial RNA processing is responsible for cleaving RNA transcripts to form the primers necessary for mtDNA replication [21]. Recently, a thermogenic coactivator, PGC-1, has also been shown to stimulate mitochondrial biogenesis by increasing the expression of NRF-1 and NRF-2. NRF-2 binding sites are present in the upstream regions of many nuclear-encoded mitochondrial proteins, including cytochrome c oxidase subunits IV and Vb, ATP synthase β -subunit, and human Tfam [17, 18]. Genes that encode mitochondrial oxida-

tive phosphorylation proteins and Tfam also have binding sites for the transcription factor Sp1 in their promoter region [18, 22]. Sp1 is known to bind to GC-rich *cis*-elements [23, 24] and may compete with the zinc finger transcription factor Egr-1 for similar promoter sites [25, 26].

It is now well established that mitochondrial proteins are imported into the organelle posttranslationally. Mitochondria of the yeast *Saccharomyces cerevisiae* contain at least 750 different proteins, which perform diverse roles. Most of these proteins (approximately 99%) are translated on cytosolic ribosomes, and their import into mitochondria is essential for mitochondrial function. Further, the proteinaceous machineries of great complexity, the so-called translocases, in the mitochondrial membranes mediate the import of these proteins [27]. Following synthesis in the cytosol, mitochondrial preproteins are stabilized in an import-competent manner by cytosolic chaperones, such as the heat shock protein 70 (HSP70). This allows for the positively charged presequence to interact with acidic regions on the import receptor Tom20-Tom22 (translocase of the outer membrane). HSP70 is then released in an ATP-independent manner and the precursor is inserted into the outer mitochondrial membrane [28, 29]. In addition to the HSP70 chaperone pathway, preproteins containing internal targeting sequences interact with a chaperone mitochondrial import-stimulating factor that binds specifically to the import receptor Tom70-Tom37, and transfers the precursor to this subcomplex through the hydrolysis of ATP [28, 29]. The inner mitochondrial membrane uniquely contains the acidic phospholipid cardiolipin, which is believed to aid the import process [30]. The translocase protein complexes of the inner mitochondrial membrane are called the Tim proteins (translocase of the inner membrane) [31], which form a pore across the inner membrane consisting of Tim23 and Tim17, and guide the positively charged presequence across the polarized inner membrane [32, 33]. The mitochondrial inner membrane imports numerous proteins that span it multiple times using the membrane potential $\Delta\psi$ as the only external energy source. Rehling et al. [34] have shown that protein insertion complex (TIM22 complex), a twin-pore translocase, mediates the insertion of precursor proteins in a three-step process. After the precursor is tethered to the translocase without losing energy from the $\Delta\psi$, two energy-requiring steps, namely action of $\Delta\psi$ on the precursor protein to promote its docking in the translocase complex and then, $\Delta\psi$ and an internal signal peptide, together induce rapid gating transitions in one

pore and closing of the other pore and drive membrane insertion to completion. Upon arrival in the matrix, the presequence is cleaved by the mitochondrial processing peptidase, and the mature protein is folded into its proper conformation by the chaperones mtHSP70, HSP60 and/or chaperonin 10.

Activation of transcription factors and mitochondrial biogenesis are now known to be affected by a number of inherited genetic defects. A number of mitochondrial diseases associated with mtDNA defects ranging from point mutations to large-scale deletions or marked reduction in mtDNA quantity (depletion) form a group of neurogenetic disorders called neuromuscular diseases [35]. Point mutations in mtDNA that lead to mitochondrial disorders are maternally inherited and tend to cause a wide spectrum of clinical phenotypes [36]. Leigh's diseases and Leber's hereditary optical neuropathy are caused by point mutations in mtDNA genes and have a broad spectrum of clinical defects such as encephalomyopathies, ataxia, cardiomyopathy or sensorineural hearing loss [37, 38]. Major deletions in mtDNA have also been reported to occur that cause diseases of skeletal muscle, mitochondrial encephalomyopathies and cardiomyopathies. Kearns-Sayre syndrome, progressive external ophthalmoplegia and Pearson's marrow syndrome are the result of large-scale single mtDNA deletions and impairment of mitochondrial protein synthesis [39]. A significant reduction in mtDNA, also called depletion of mtDNA and characterized by a concomitant reduction in respiratory complex activities, has been reported to cause congenital or infantile myopathies. Studies investigating mitochondrial myopathies with depleted mtDNA have reported a corresponding reduction in Tfam protein and mRNA [40, 41]. On the other hand, mitochondrial diseases caused by an accumulation (duplication) of mtDNA are also known and muscle fibers from 2 patients with an accumulation of mtDNA have been shown to contain an elevated amount of Tfam protein [40] as well. The nuclear genome, which encodes most of the proteins involved in biogenesis of mitochondria, has also been linked to mtDNA defects and related myopathies [42]. Mutations in nuclear genes that encode structural subunits of respiratory oxidative phosphorylation complexes I–III have been reported to cause Leigh syndrome or Leigh syndrome-like disorders where patients are presented with lactic acidosis and progressive neurodegeneration of variable onset. Nuclear genes encoding proteins required in assembly of respiratory complexes or maintenance of mtDNA have also been linked to encephalocardiomyopathies.

As the new information on molecular mechanisms of mitochondrial biogenesis is rapidly emerging, the role of nuclear and mitochondrial genes in mitochondrial dysfunction and related neuromuscular disorders is becoming clearer. Recent reports [43, 44] on the regulation of mitochondrial biogenesis by cytokines such as nitric oxide propose a new insight into the complex process of mitochondrial biogenesis. The fact that NO, a versatile molecule in human pathophysiology due to its myriad of regulatory effects on different types of cells, promotes mitochondrial biogenesis leads us into a new direction for studying mechanisms of neuromuscular disorders and provides new hope for cure or prevention of diseases with mitochondrial dysfunction.

Lysosome Biogenesis and Metabolic Diseases

Lysosomes are membrane-bound cytoplasmic organelles that receive membrane traffic input from the biosynthetic, endocytic and autophagic pathways, and serve as major degradative compartments in the eukaryotic cells [45]. The degradative function of these organelles is carried out by more than 50 acid-dependent hydrolases (e.g. proteases, lipases, glycosidases) contained within its lumen [46]. The limiting membrane of the lysosome contains highly glycosylated proteins, lysosomal-associated membrane proteins (LAMPs) such as LAMP-1, LAMP-2, and CD63/LAMP-3, in addition to the proteins that mediate transport of ions, amino acids, and other solutes across the lysosomal membrane and contribute to the maintenance of an acidic luminal pH in the range of 4.6–5.0 [47]. The lack of cation-dependent and cation-independent mannose-6-phosphate receptors (MPRs) in lysosomal membrane distinguishes lysosomes from late endosomal compartments, and lysosomes share this characteristic with lysosome-related organelles, a group of cell type-specific nondegradative bodies that includes melanosomes, lytic granules, major histocompatibility complex class II compartments, platelet-dense granules, basophil granules, and neutrophil azurophil granules [48, 49]. The physiological importance of lysosomes and related organelles is evidenced by the myriad of diseases resulting from defects in their biogenesis and function [50, 51]. Lysosomal biogenesis is an orchestration of the structural and functional elements of the lysosome to form an integrated organelle and involves the synthesis, targeting, functional residence, and turnover of the proteins that comprise the lysosome. The question of how lysosomes form has captivated the interest of cell biolo-

gists for decades and the known molecular mechanisms of lysosome biogenesis are believed to involve vesicular delivery of newly synthesized lysosomal proteins from the trans-Golgi network (TGN), fusion of lysosomes with late endosomes and sorting of membrane proteins into luminal vesicles [52]. A cascade of events that leads to biogenesis of lysosomes include the formation of early endosomes by coalescence of vesicles from the plasma membrane, the removal of recycling vesicles and addition of TGN-derived vesicles to convert these endosomes to late endosomes, and eventually to lysosomes [53, 54]. Alternatively, the early endosomes, late endosomes and lysosomes are considered stable compartments and transport proceeding from early endosomes through an endosomal carrier vesicle with characteristics of a multivesicular body to late endosomes leads to mature lysosomes [55, 56].

Though different mechanisms have been proposed, yet the complexity of events involved in lysosomal biogenesis remains unresolved. For any model of lysosomal biogenesis to work, a mechanism for selective sorting of materials bound for lysosomes must exist and most newly synthesized lysosomal proteins are directed to lysosomes through an MPR-dependent or MPR-independent fashion [57]. The sorting of MPRs and lysosomal membrane proteins is mediated by signals present in the cytoplasmic domains that are recognized by cytosolic molecules recruited onto membranes at sites of vesicle formation (e.g. the TGN, plasma membrane and endosomes). A number of heterotetrameric adaptor protein (AP) complexes, AP-1, AP-2, AP-3 and AP-4, mediate transport of MPRs and lysosomal integral membrane proteins from the TGN to endosomes [58, 59]. AP-1 has been suggested to play a role in recycling MPRs from endosomes to the TGN. Two unrelated connector molecules, TIP47 [60] and PACS-1 [61], have also been implicated in recycling of MPRs to the TGN. Recent studies have identified a novel family of coat proteins, termed GGAs, which may be involved in biosynthetic protein transport from the TGN to the endosomal/lysosomal system. The recruitment of GGAs to the TGN appears to be mediated by members of the ADP-ribosylation factor family of proteins. Once carrier vesicles are formed and cargo proteins sorted into them, the vesicles need to be targeted and eventually fuse with acceptor compartments. GTP-binding proteins, called rabs, found at the plasma membrane and on organelles of secretory nature appear to be required for transport of MPRs to the lysosome [62]. Targeting and membrane fusion also require vesicle-associated membrane proteins collectively known as N-ethyl-

maleimide-sensitive factor attachment protein receptors, or SNAREs, and are found on both vesicles (v-SNAREs) and target membranes (t-SNAREs) [63]. The degree to which these, or other, mammalian SNAREs are required for sorting to the mature lysosome itself remains uncertain. Recent studies on lysosomal targeting have revealed a variety of proteins as components of the lysosome biogenesis machinery, and the establishment of physical and/or functional relationships between them will undoubtedly clarify understanding of lysosome biogenesis.

Advances in understanding the complexities of lysosomal biogenesis, lysosomal hydrolase sorting and hydrolytic requirements have led to the possibility of a successful enzyme therapy for lysosomal storage disorders, a group of over 45 distinct genetic diseases resulting from a deficiency of a particular lysosomal protein or, in a few cases, from nonlysosomal proteins that are involved in lysosomal biogenesis [64, 65]. Lysosomal enzymes sialidase (α -neuraminidase), β -galactosidase, and N-acetylaminogalacto-6-sulfate sulfatase are involved in the catabolism of glycolipids, glycoproteins, and oligosaccharides. Their functional activity in the cell depends on their association in a multienzyme complex with lysosomal carboxypeptidase, and cathepsin A and the integrity of the complex plays a crucial role at different stages of biogenesis of lysosomal enzymes, including intracellular sorting and proteolytic processing of their precursors [66]. The complex plays a protective role for all components, extending their half-life in the lysosome from several hours to several days, and for sialidase, the association with cathepsin A is also necessary for the expression of enzymatic activity. The disintegration of the complex due to genetic mutations in its components results in their functional deficiency and causes severe metabolic disorders: sialidosis (mutations in sialidase), GM1 gangliosidosis and Morquio disease type B (mutations in β -galactosidase), galactosialidosis (mutations in cathepsin A), and Morquio disease type A (mutations in N-acetylaminogalacto-6-sulfate sulfatase) [67–70].

Most of the properties of lysosomes are shared with a group of cell type-specific compartments referred to as 'lysosome-related organelles', which include melanosomes, lytic granules, major histocompatibility complex class II compartments, platelet dense granules, basophil granules and azurophil granules. In addition to lysosomal proteins, these organelles contain cell type-specific components that are responsible for their specialized functions. Abnormalities in both lysosomes and lysosome-related organelles have been observed in human genetic diseases such as the Chediak-Higashi and Her-

mansky-Pudlak syndromes [71–72]. Identification of genes mutated in these human diseases is beginning to shed light on the molecular machinery involved in the biogenesis of lysosomes and lysosome-related organelles.

Peroxisomes and Peroxisomal Biogenesis Disorders

Peroxisomes, the single-membrane-bound cell organelles also called microbodies, are now known to contain more than 60 different enzymes that carry out a number of important metabolic pathways including β -oxidation of very long chain fatty acids, synthesis of plasmalogens and degradation of reactive oxygen species [73, 74]. Metabolic functions of peroxisomes are vital for cell survival and the importance of peroxisomes in human health was highlighted in the late 1980s with recognition of a number of inherited fatal metabolic diseases with dysfunction of this organelle [75, 76]. Peroxisomal disorders, a relatively new category of inherited metabolic diseases, occur due to a defect in either the assembly of the organelle or import of peroxisomal proteins into the organelle. Biogenesis of peroxisomes maintains the required number and size of peroxisomes in the tissues according to the metabolic milieu [77]. Peroxisome biogenesis conceptually consists of (a) the formation of the peroxisomal membrane, (b) the import of proteins into the peroxisomal matrix and (c) proliferation of the organelles [78]. As a result of combined genetic and biochemical approaches, 32 genes have been identified that encode proteins involved in peroxisome biogenesis [79, 80]. These genes are called *PEX* genes and their protein products are termed peroxins. Elaborate peroxin complexes form the receptor machinery, which in a concerted action of the components transports folded, even oligomeric matrix proteins across the peroxisomal membrane. The past decade has significantly improved our knowledge of peroxins, which can now be clearly divided into two distinct groups: those involved exclusively in peroxisome matrix protein import, and those involved in peroxisome membrane biogenesis.

Of the above steps of peroxisome biogenesis, the most is understood about matrix protein import. Matrix proteins are encoded by nuclear genes, synthesized on free ribosomes in the cytoplasm and imported into the peroxisome posttranslationally. Two targeting signals for peroxisomal matrix proteins have been identified [81]. The most commonly used signal is the peroxisomal targeting

Table 1. Summary of classical mitochondrial, lysosomal and peroxisomal biogenesis disorders, their clinical characteristics and related defective genes

Inherited diseases	Clinical symptoms	Gene(s)
<i>Mitochondrial biogenesis disorders</i>		
Leigh's syndrome	bilateral lesions in basal ganglia, ataxia, seizures, hypotonia, lactic acidosis, developmental delay, hypertrophic cardiomyopathy	<i>mtDNA</i> deletion
Progressive external ophthalmoplegia	hypotonia, developmental delay, lactic acidosis, progressive ophthalmoplegia (external)	<i>mtDNA</i> deletion
<i>Lysosomal biogenesis disorders</i>		
Chediak-Higashi syndrome	progressive neurological impairment, bleeding diathesis, severe immunological deficiency, hypopigmentation of skin, hair and eyes	<i>CHS1</i>
Hermansky-Pudlak syndrome	oculocutaneous albinism, ceroid lipofuscinosis, prolonged bleeding	<i>HPS1</i>
<i>Peroxisomal biogenesis disorders</i>		
Zellweger syndrome	dysmorphic features, hypotonia, developmental delay, seizures, failure to thrive, hepatomegaly, psychomotor retardation	<i>PEX1</i>

signal 1, or PTS1, which consists of a conserved tripeptide at the extreme C terminus of a protein of consensus sequence Ser-Lys-Leu-COOH. The second targeting signal is the peroxisomal targeting signal 2, or PTS2, which must be present at the N terminus of a protein, and thiolase presents the best example of a peroxisomal protein with PTS2. The targeting signals are recognized by specific receptor proteins, the peroxins (PEX), present on the peroxisomal membrane or in the cytosol as carriers. PEX5 recognizes PTS1, while PEX7 binds PTS2, and these receptors bind their cargo in the cytoplasm, possibly with the aid of chaperone proteins [82]. Very little is known about how the receptors transport their cargo to the peroxisome. The receptors have been reported to interact with PEX13, suggesting that PEX13 is a member of the receptor docking complex. PEX14 has also been reported as equally important for the docking process of PTS receptors. PEX17 is also thought to be part of the docking complex and associates directly with PEX14. PEX10 and PEX12 are integral peroxisome membrane proteins, which have been shown to directly interact and are members of the putative translocation apparatus, along with PEX2 and PEX8. PEX3 has been shown to act as a putative peroxisomal receptor for PEX19. PEX12 and PEX8 have both been demonstrated to interact with PEX5. PEX5 has been demonstrated to be a cycling receptor and this recycling is thought to be mediated by the AAA ATPases PEX1 and PEX6, the ubiquitin-conjugating enzyme PEX4, and the putative docking site for PEX4, PEX22, PEX15 and PEX27 have recently been suggested

to also act as binding partners for AAA peroxins at the peroxisomal membrane [83].

To date, only 3 peroxins have been directly implicated in the formation of peroxisomal membranes during peroxisome biogenesis. PEX3, PEX16, and PEX19 are the 3 proteins identified to be involved in the process of the formation of peroxisome membranes de novo [84]. PEX19 is the only peroxin known to directly bind the majority of known peroxisomal membrane proteins, and there are possibly other cytoplasmic proteins which aid PEX19 in the cytoplasmic portion of the peroxisome biogenesis process (i.e. chaperone proteins), but these proteins have not yet been identified. PEX11 is considered to be required for peroxisome proliferation since overexpression of PEX11 causes massive proliferation of peroxisomes. PEX11b is expressed constitutively, suggesting a general role in the maintenance of peroxisome number, whereas PEX11a is inducible, and can cause peroxisome proliferation in response to external stimuli [85].

Disorders of peroxisome biogenesis are multiorgan diseases and the nervous system is implicated in most of them. On a genetic basis, complementation of fibroblasts has classified peroxisome biogenesis disorders [86] into 12 complementation groups. Identification of peroxisome biogenesis genes (PEX) has, however, led to a new association of peroxisome biogenesis disorders with gene defects. Zellweger syndrome (also referred to as cerebro-hepato-renal syndrome), neonatal adrenoleukodystrophy, and infantile Refsum disease along with rhizomelic chondrodysplasia punctata are autosomal recessive diseases

collectively called the peroxisome biogenesis disorders. The biochemical phenotype of these disorders is reflective of the defect in peroxisome biogenesis as demonstrated by increased levels of very long chain fatty acid and phytanic acid, and reduced plasmalogen levels [87]. There are also high levels of the bile acid intermediates as well as increased levels of the lysine metabolite pipelicolic acid. Zellweger syndrome belongs to complementation group 1, which is caused by mutations in *PEX1* [88]. Within this complementation group, there are 2 common mutations, which together comprise 60% of the alleles in the complementation group. One is a mutation which causes the amino acid change G843D, and this is associated with the milder phenotypes of the Zellweger spectrum. The other, a frameshift in exon 13 of *PEX1*, is associated with the severe phenotype of Zellweger syndrome [89]. Rhizomelic chondrodysplasia punctata results from a defect in *PEX7*, the PTS2 receptor [90]. Because this receptor is only required for the import of PTS2-containing proteins, of which there are only 3 known in humans (thiolase, phytanoyl-CoA hydroxylase, and dihydroxyacetonephosphate synthase), a defect in this protein produces a very different clinical phenotype from that of the Zellweger spectrum. The biochemical phenotype of rhizomelic chondrodysplasia punctata also reflects the molecular basis of the disease [91]. Patients have a defect in branched-chain fatty acid metabolism as well as a defect in plasmalogen biosynthesis, but lack the other biochemical defects present in the Zellweger spectrum.

Primary hyperoxaluria type I [92] presents a unique peroxisomal disorder where targeting of alanine:glyoxylate aminotransferase, a peroxisomal enzyme, to mitochondria instead of peroxisome leads to urolithiasis and/or nephrocalcinosis.

In summary, molecular organization of subcellular organelles is key to their specific metabolic functions in the cell. Biogenesis of subcellular organelles determines the cellular metabolic state, which in turn maintains the physiologic functions of the tissue, leading to a pathological condition. Biogenesis of mitochondria, peroxisomes, lysosomes, endoplasmic reticulum and other subcellular organelles is tightly controlled by a complex network of events that involve the transcriptional regulation of the expression of organellar proteins, their posttranscriptional modifications, import into the organelle for structural organization and their intermolecular interaction. A defect in any of the components of this network leads to a serious pathological state of mitochondrial or lysosomal or peroxisomal diseases. Recent information on molecular mechanisms of organelle biogenesis has unraveled to some extent the complexity of interorganellar interactions as well, where an abnormal biogenesis of one organelle will affect biogenesis of the other organelle(s). A better understanding of the molecular mechanisms of organellar biogenesis has not only unraveled the pathogenic mechanisms of metabolic disorders but has also provided new tools for correcting the metabolic defects and related complications.

References

- 1 Nunnari J, Walter P: Regulation of organelle biogenesis. *Cell* 1996;84:389–394.
- 2 Warren G, Wickner W: Organelle inheritance. *Cell* 1996;84:395–400.
- 3 Hill C, Treisman R: Transcriptional regulation by extracellular signals: Mechanisms and specificity. *Cell* 1995;80:199–211.
- 4 Palade G: Membrane biogenesis: An overview. *Methods Enzymol* 1983;96:29–55.
- 5 Anderson S, Bankier AT, Barrel BG, de Bruijn MH, Coulson AR, Drouin J, Eperon IC, et al: Sequence and organization of the human mitochondrial genome. *Nature* 1981;290:457–465.
- 6 Marin-Garcia J, Goldenthal MJ: Mitochondrial biogenesis defects and neuromuscular disorders. *Pediatr Neurol* 2000;22:122–129.
- 7 Lazarow PB, Fujiki Y: Biogenesis of peroxisomes. *Annu Rev Cell Biol* 1986;1:489–530.
- 8 Lazarow PB, Moser HW: Disorders of peroxisome biogenesis; in Scriver CR, et al (eds): *The Metabolic and Molecular Bases of Inherited Disease*. New York, McGraw-Hill, 1995, pp 2287–2324.
- 9 Tager JM: Inborn errors of cellular organelles: An overview. *J Inher Metab Dis* 1987;10 (Suppl1):3–10.
- 10 Walter P, Johnson AE: Signal sequence recognition and protein targeting to the endoplasmic reticulum membrane. *Annu Rev Cell Biol* 1994;10:87–119.
- 11 Ryan KR, Jensen RE: Protein translocation across mitochondrial membranes: What a long, strange trip it is. *Cell* 1995;83:517–519.
- 12 Senior AE: ATP synthesis by oxidative phosphorylation. *Physiol Rev* 1988;68:177–230.
- 13 Orenius S: Mitochondrial regulation of apoptotic cell death. *Toxicol Lett* 2004;149:19–23.
- 14 Kluck RM, Bossy-Wetzel E, Green DR, Newmeyer DD: The release of cytochrome c from mitochondria: A primary site for Bcl-2 regulation of apoptosis. *Science* 1997;275:1132–1136.
- 15 Chang DD, Clayton DA: Priming of human mitochondrial DNA replication occurs at the light-strand promoter. *Proc Natl Acad Sci USA* 1985;82:351–355.
- 16 Fisher RP, Clayton DA: Purification and characterization of human mitochondrial transcription factor 1. *Mol Cell Biol* 1988;8:3496–3509.
- 17 Virbasius JV, Scarpulla RC: Activation of the human mitochondrial transcription factor A gene by nuclear respiratory factors: A potential regulatory link between nuclear and mitochondrial gene expression in organelle biogenesis. *Proc Natl Acad Sci USA* 1994;91:1309–1313.

- 18 Scarpulla R: Nuclear control of respiratory chain expression in mammalian cells. *J Bioenerg Biomembr* 1997;29:109-119.
- 19 Gugneja S, Scarpulla RC: Serine phosphorylation within a concise amino-terminal domain in nuclear respiratory factor 1 enhances DNA binding. *J Biol Chem* 1997;272:18732-18739.
- 20 Gugneja S, Vibasius CA, Scarpulla RC: Nuclear respiratory factors 1 and 2 utilize similar glutamine-containing clusters of hydrophobic residues to activate transcription. *Mol Cell Biol* 1996;16:5708-5716.
- 21 Clayton DA: Transcription and replication of animal mitochondrial DNAs. *Int Rev Cytol* 1992;141:217-232.
- 22 Lenka N, Vijayasarathy C, Mullick J, Avadhani NG: Structural organization and transcription regulation of nuclear genes encoding the mammalian cytochrome c oxidase complex. *Prog Nucleic Acid Res Mol Biol* 1998;61:309-344.
- 23 Berg JM: Sp1 and the subfamily of zinc finger proteins with guanine-rich binding sites. *Proc Natl Acad Sci USA* 1992;89:11109-11110.
- 24 Phillipsen S, Suske G: A tale of three fingers: The family of mammalian Sp/XKLF transcription factors. *Nucleic Acids Res* 1999;27:2991-3000.
- 25 Huang RP, Fan Y, Ni Z, Mercola D, Adamson ED: Reciprocal modulation between Sp1 and Egr-1. *J Cell Biochem* 1997;66:489-499.
- 26 Silverman ES, Khachigian LM, Lindner V, Williams AJ, Collins T: Inducible PDGF A-chain transcription in smooth muscle cells is mediated by Egr-1 displacement of Sp1 and Sp3. *Am J Physiol* 1997;273:H1415-H1426.
- 27 Chacinska A, Rehling P: Moving proteins from the cytosol into mitochondria. *Biochem Soc Trans* 2004;32:774-776.
- 28 Komiya T, Sakaguchi M, Mihara K: Cytoplasmic chaperones determine the targeting pathway of precursor proteins to mitochondria. *EMBO J* 1996;15:399-407.
- 29 Komiya T, Rospert S, Schatz G, Mihara K: Binding of mitochondrial precursor proteins to the cytoplasmic domains of the import receptors Tom70 and Tom20 is determined by cytoplasmic chaperones. *EMBO J* 1997;16:4267-4275.
- 30 Eilers M, Endo T, Schatz G: Adriamycin, a drug interacting with acidic phospholipids, blocks import of precursor proteins by isolated yeast mitochondria. *J Biol Chem* 1989;264:2945-2950.
- 31 Pfanner N, Douglas MG, Endo T, Hoogenraad NJ, Jensen RE, Meijer M, Neupert W, Schatz G, Schmitz UK, Shore GC: Uniform nomenclature for the protein transport machinery of the mitochondrial membranes. *Trends Biochem Sci* 1996;21:51-52.
- 32 Pfanner N, Meijer M: Mitochondrial biogenesis: The Tom and Tim machine. *Curr Biol* 1997;7:R100-R103.
- 33 Schatz G: The protein import system of mitochondria. *J Biol Chem* 1996;271:31763-31766.
- 34 Rehling P, Brandner K, Pfanner N: Mitochondrial import and the twin-pore translocase. *Nat Rev Mol Cell Biol* 2004;5:519-530.
- 35 Larsson N, Clayton DA: Molecular genetic aspects of human mitochondrial disorders. *Annu Rev Genet* 1995;29:151-178.
- 36 Schon EA, Bonilla E, DiMauro S: Mitochondrial DNA mutations and pathogenesis. *J Bioenerg Biomembr* 1997;29:131-149.
- 37 Corona P, Lamantea E, Greco M: Novel heteroplasmic mtDNA mutation in a family with heterogeneous clinical presentations. *Ann Neurol* 2002;51:118-122.
- 38 Santorelli FM, Mak SC, El-Schahawi M: Maternally inherited cardiomyopathy and hearing loss associated with a novel mutation in the mitochondrial tRNA(Lys) gene (G8363A). *Am J Hum Genet* 1996;58:933-939.
- 39 Holt IJ, Harding AE, Morgan-Hughes JA: Deletions of mtDNA in patients with mitochondrial myopathies. *Nature* 1988;331:717-719.
- 40 Larsson N, Oldfors A, Holme E, Clayton DA: Low levels of mitochondrial transcription factor A in mitochondrial DNA depletion. *Biochem Biophys Res Commun* 1994;200:1374-1381.
- 41 Poulton J, Morten K, Freeman-Emmerson C, Potter C, Sewry C, Dubowitz V, Kidd H, Stephenson J, Whitehouse W, Hansen FJ, Parisi M, Brown G: Deficiency of the human mitochondrial transcription factor h-mtTFA in infantile mitochondrial myopathy is associated with mtDNA depletion. *Hum Mol Genet* 1994;3:1763-1769.
- 42 Goffart S, Wiesner RJ: Regulation and co-ordination of nuclear gene expression during mitochondrial biogenesis. *Exp Physiol* 2003;88:33-40.
- 43 Nisoli E, Clementi E, Paolucci C, Cozzi V, Tonello C, Sciorati C, Bracale R, Valero A, Francolini M, Moncada S, Carruba MO: Mitochondrial biogenesis in mammals: The role of endogenous nitric oxide. *Science* 2003;299:896-899.
- 44 Leary SC, Shoubridge EA: Mitochondrial biogenesis: Which part of 'NO' do we understand? *Bioessays* 2003;25:538-541.
- 45 Griffiths G: What's special about secretory lysosomes? *Semin Cell Dev Biol* 2002;13:279-84.
- 46 de Duve C: The lysosome concept; in de Reuck AVS, Cameron MP (eds): *Lysosomes*. Boston, Little Brown, 1963, pp 1-35.
- 47 Eskelinen EL, Tanaka Y, Saftig P: At the acidic edge: Emerging functions for lysosomal membrane proteins. *Trends Cell Biol* 2003;13:137-145.
- 48 Orlow SJ: Melanosomes are specialized members of the lysosomal lineage of organelles. *J Invest Dermatol* 1995;105:3-7.
- 49 Griffiths GM, Argon Y: Structure and biogenesis of lytic granules. *Curr Top Microbiol Immunol* 1995;198:39-58.
- 50 Spritz RA: Multi-organellar disorders of pigmentation: Tied up in traffic. *Clin Genet* 1999;55:309-317.
- 51 Meikle PJ, Hopwood JJ: Lysosomal storage disorders: Emerging therapeutic options require early diagnosis. *Eur J Pediatr* 2003;162(Suppl 1):S34-S37.
- 52 Mullins C, Bonifacino JS: The molecular machinery for lysosome biogenesis. *Bioessays* 2001;23:333-343.
- 53 Murphy RF: Maturation models for endosome and lysosome biogenesis. *Trends Cell Biol* 1991;1:77-82.
- 54 Storrie B, Desjardins M: The biogenesis of lysosomes: Is it a kiss and run, continuous fusion and fission process? *Bioessays* 1996;18:895-903.
- 55 Dell'Angelica EC, Mullins C, Caplan S, Bonifacino JS: Lysosome-related organelles. *FASEB J* 2000;14:1265-1278.
- 56 Luzio JP, Rous BA, Bright NA, Pryor PR, Mullock BM, Piper RC: Lysosome-endosome fusion and lysosome biogenesis. *J Cell Sci* 2000;113:1515-1524.
- 57 Hunziker W, Geuze HJ: Intracellular trafficking of lysosomal membrane proteins. *Bioessays* 1996;18:379-389.
- 58 Bonifacino JS, Dell'Angelica EC: Molecular bases for the recognition of tyrosine based sorting signals. *J Cell Biol* 1999;145:923-926.
- 59 Kirchhausen T: Adaptors for clathrin-mediated traffic. *Annu Rev Cell Dev Biol* 1999;15:705-732.
- 60 Diaz E, Pfeffer SR: YIP47: A cargo selection device for mannose-6-phosphate receptor trafficking. *Cell* 1998;93:433-443.
- 61 Wan L, Molloy SS, Thomas L, Liu G, Xiang Y, Rybak SL, Thomas G: PACS-1 defines a novel gene family of cytosolic sorting proteins required for trans-Golgi network localization. *Cell* 1998;94:205-216.
- 62 Press B, Feng Y, Hoflack B, Wandinger-Ness A: Mutant Rab7 causes the accumulation of cathepsin D and cation-independent mannose-6-phosphate receptor in an early endocytic compartment. *J Cell Biol* 1998;140:1075-1089.
- 63 Pfeffer SR: Transport-vesicle targeting: Tethers before SNAREs. *Nat Cell Biol* 1999;1:E17-E22.
- 64 Grabowski GA, Hopkin RJ: Enzyme therapy for lysosomal storage disease: Principles, practice, and prospects. *Annu Rev Genomics Hum Genet* 2003;4:403-436.
- 65 Meikle PJ, Fuller M, Hopwood JJ: Mass spectrometry in the study of lysosomal storage disorders. *Cell Mol Biol* 2003;49:769-777.
- 66 Pshzhetsky AV, Ashmarina M: Lysosomal multienzyme complex: Biochemistry, genetics, and molecular pathophysiology. *Prog Nucleic Acid Res Mol Biol* 2001;69:81-114.
- 67 Strehle EM: Sialic acid storage disease and related disorders. *Genet Test* 2003;7:113-121.
- 68 Callahan JW: Molecular basis of GM1 gangliosidosis and Morquio disease, type B. Structure-function studies of lysosomal beta-galactosidase and the non-lysosomal beta-galactosidase-like protein. *Biochim Biophys Acta* 1999;1455:85-103.

- 69 Hiraiwa M: Cathepsin A/protective protein: An unusual lysosomal multifunctional protein. *Cell Mol Life Sci* 1999;56:894–907.
- 70 Pshzhetsky AV, Potier M: Association of N-acetylgalactosamine-6-sulfate sulfatase with the multienzyme lysosomal complex of beta-galactosidase, cathepsin A, and neuraminidase. Possible implication for intralysosomal catabolism of keratan sulfate. *J Biol Chem* 1996;271:28359–28365.
- 71 Dell'Angelica EC, Mullins C, Caplan S, Bonifacio JS: Lysosome-related organelles. *FASEB J* 2000;14:1265–1278.
- 72 Kjeldsen L, Calafat J, Borregaard N: Giant granules of neutrophils in Chediak-Higashi syndrome are derived from azurophil granules but not from specific and gelatinase granules. *J Leukoc Biol* 1998;64:72–77.
- 73 Singh I: Biochemistry of peroxisomes in health and disease. *Mol Cell Biochem* 1997;167:1–29.
- 74 Dansen TB, Wirtz KW: The peroxisome in oxidative stress. *IUBMB Life* 2001;51:223–230.
- 75 Baumgartner MR, Saudubray JM: Peroxisomal disorders. *Semin Neonatol* 2002;7:85–94.
- 76 Gartner J: Organelle disease: Peroxisomal disorders. *Eur J Pediatr* 2000;159(Suppl 3):S236–S239.
- 77 Lazarow PB: Peroxisome biogenesis: Advances and conundrums. *Curr Opin Cell Biol* 2003;15:489–497.
- 78 Brown LA, Baker A: Peroxisome biogenesis and the role of protein import. *J Cell Mol Med* 2003;7:388–400.
- 79 Vizeacoumar FJ, Torres-Guzman JC, Bouard D, Aitchison JD, Rachubinski RA: Pex30p, Pex31p and Pex32p form a family of peroxisomal integral membrane proteins regulating peroxisome size and number in *Saccharomyces cerevisiae*. *Mol Biol Cell* 2004;15:665–677.
- 80 Eckert JH, Erdmann R: Peroxisome biogenesis. *Rev Physiol Biochem Pharmacol* 2003;147:75–121.
- 81 Subramani S: Convergence of model systems for peroxisome biogenesis. *Curr Opin Cell Biol* 1996;8:513–518.
- 82 Suzuki Y, Shimozawa N, Imamura A, Fukuda S, Zhang Z, Orii T, Kondo N: Clinical, biochemical and genetic aspects and neuronal migration in peroxisome biogenesis disorders. *J Inherit Metab Dis* 2001;24:151–165.
- 83 Birschman I, Stroobants A, van den Berg M, Schafer A, Rosenkranz K, Kunau WH, Tabak H: Pex15p of *Saccharomyces cerevisiae* provides a molecular basis for recruitment of the AAA peroxin Pex6p to peroxisomal membranes. *Mol Biol Cell* 2003;14:2226–2236.
- 84 Purdue PE, Lazarow PB: Peroxisome biogenesis. *Annu Rev Cell Dev Biol* 2001;17:701–752.
- 85 Li X, Baumgart E, Dong GX, Morrell JC, Jimenez-Sanchez G, Valle D, Smith KD, Gould SJ: PEX11alpha is required for peroxisome proliferation in response to 4-phenylbutyrate but is dispensable for peroxisome proliferator-activated receptor alpha-mediated peroxisome proliferation. *Mol Cell Biol* 2002;22:8226–8240.
- 86 Gould SJ, Valle D: Peroxisome biogenesis disorders: Genetics and cell biology. *Trends Genet* 2000;16:340–345.
- 87 Gootjes J, Mooijer PA, Dekker C, Barth PG, Poll-The BT, Waterham HR, Wanders RJ: Biochemical markers predicting survival in peroxisome biogenesis disorders. *Neurology* 2002;59:1746–1749.
- 88 Preuss N, Brosius U, Biermanns M, Muntau AC, Conzelmann E, Gartner J: PEX1 mutations in complementation group 1 of Zellweger spectrum patients correlate with severity of disease. *Pediatr Res* 2002;51:706–714.
- 89 Maxwell MA, Nelson PV, Chin SJ, Paton BC, Carey WF, Crane DI: A common PEX1 frameshift mutation in patients with disorders of peroxisome biogenesis correlates with the severe Zellweger syndrome phenotype. *Hum Genet* 1999;105:38–44.
- 90 Purdue PE, Zhang JW, Skoneczny M, Lazarow PB: Rhizomelic chondrodysplasia punctata is caused by deficiency of human PEX7, a homologue of the yeast PTS2 receptor. *Nat Genet* 1997;15:381–384.
- 91 Purdue PE, Skoneczny M, Yang X, Zhang JW, Lazarow PB: Rhizomelic chondrodysplasia punctata, a peroxisomal biogenesis disorder caused by defects in Pex7p, a peroxisomal protein import receptor: A minireview. *Neurochem Res* 1999;24:581–586.
- 92 Danpure CJ: Primary hyperoxaluria; in Scriver CR, et al (eds): *The Metabolic and Molecular Bases of Inherited Disease*. New York, McGraw-Hill, 2001, pp 3323–3367.