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Review

Molecular and cellular basis of lysosomal transmembrane protein dysfunction

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ClC-7
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TRPML1
Mucolipin
LAMP2

ABSTRACT

Lysosomal membrane proteins act at several crucial steps of the lysosome life cycle, including lumen acidification, metabolite export, molecular motor recruitment and fusion with other organelles. This review summarizes the molecular mechanisms of lysosomal storage diseases caused by defective transport of small molecules or ions across the lysosomal membrane, as well as Danon disease. In cystinosis and free sialic acid storage diseases, transporters for cystine and acidic monosaccharides, respectively, are blocked or retarded. A putative cobalamin transporter and a hybrid transporter/transferase of acetyl groups are defective in cobalamin F type disease and mucopolysaccharidosis type IIIC, respectively. In neurodegenerative forms of osteopetrosis, mutations of a proton/chloride exchanger impair the charge balance required for sustained proton pumping by the V-type ATPase, thus resulting in bone-resorption lacuna neutralization. However, the mechanism leading to lysosomal storage and neurodegeneration remains unclear. Mucolipidosis type IV is caused by mutations of a lysosomal cation channel named TRPML1; its gating properties are still poorly understood and the ion species linking this channel to lipid storage and membrane traffic defects is debated. Finally, the autophagy defect of Danon disease apparently arises from a role of LAMP2 in lysosome/autophagosome fusion, possibly secondary to a role in dynein-based centripetal motility.

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1. Introduction

Lysosomes are intracellular hydrolytic organelles able to degrade a wide variety of macromolecules as well as whole damaged organelles. This potent and versatile degradative power is segregated from other cell constituents by a phospholipid membrane, which requires proteins to fulfil diverse molecular functions. Lysosomes are acidified by a V-type H^+-ATPase to promote enzymatic activity and control biogenesis steps such as the maturation of hydrolytic enzymes [1]. Lysosomal catabolites produced in the lumen are exported to the cytosol by membrane transporters to allow their reuse in cell metabolism [2]. These transporters are generally driven by the proton gradient created by the V-ATPase. Some transporters import macromolecules into the lumen to promote their degradation. Membrane fusion and fission events are required during lysosomal biogenesis or for the interaction of lysosomes with their target organelles, i.e., endosomes, autophagosomes, phagosomes and plasma membrane [3]. These membrane traffic events are controlled by complex protein machineries. Finally, before fusing with their target organelles, lysosomes move along microtubules, a process which requires the recruitment of molecular motors to their membrane.

Among the ~50 known lysosomal storage diseases, a few are caused by lysosomal membrane protein dysfunction (Table 1). This number may increase in the future with a better characterization of the lysosomal membrane proteome [4,5]. Except for mucopolysaccharidosis type IIIC which is caused by mutations of an enzyme using cytosolic acetyl-coenzyme A to acetylate intralysosomal α-glucosamine residues [6,7], all lysosomal membrane diseases listed in Table 1 are primarily caused by nonenzymatic defects.

This review focuses on the molecular function and dysfunction of lysosomal transporters and channels as well as the molecular pathophysiology of Danon disease. Although the neuronal ceroid lipofuscinosis subtypes associated with CLN7 and CLN3 defects may

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Table 1
Genetic and molecular features of lysosomal storage diseases caused by defects in lysosomal membrane proteins

Human disease	OMIM #	Inheritance	Causative gene, locus	Protein name (aliases)	Protein size, # of transmembrane helices (TM)	Molecular function	Substrates	Animal models	Other genetic models
Cystinosis	219800 (infantile) 219900 (juvenile) 219750 (adult, nonnephropathic)	Autosomal recessive	*CTNS*, 17p13 [17]	Cystinosin	367 aa; 7 TM	H^+/amino acid symport [19]	L-cystine	Mouse KO [23]	*S. cerevisiae* (ERS1) [155]
Salla disease Infantile sialic acid storage disorder	604369 269920	Autosomal recessive	*SLC17A5*, 6q14–q15 [42]	Sialin	495 aa; 12 TM	H^+/sugar symport [47,48], vesicular amino acid import [57]	Sialic acids, acidic hexoses (organelle export) Aspartate, glutamate (import)	None	
Cobalamin F-type disease	277380	Autosomal recessive	*LMBRD1*, 6q13 [171]	LMBD1	540 aa; 9 TM	Membrane transport (predicted) [64]	Cobalamin (predicted)	None	
Neuronal ceroid lipofuscinosis, late infantile variant	610951	Autosomal recessive	*MFSD8*, 4q28.1–q28.2 [10]	CLN7	518 aa; 12 TM	Membrane transport (predicted)	Unknown	None	
Neuronal ceroid lipofuscinosis, juvenile form	204200	Autosomal recessive	*CLN3*, 16p12.1 [156]	CLN3 (Battenin)	438 aa; 6 TM	Unknown	Unknown	Mouse KO and KI [157–159]	*S. cerevisiae* (BTN1) [160], *S. pombe* (BTN1) [161]
Malignant infantile osteopetrosis	611490 259700	Autosomal recessive Autosomal recessive	*CLCN7*, 16p13 [83] *OSTM1*, 6q21 [82]	ClC-7 OSTM1	805 aa; 18 TM[a] 338 aa; 1 TM	H^+/anion antiport [87] ClC-7 ancillary subunit [79]	Cl^- N.A.	Mouse KO [80,83] Mouse grey-lethal line [82]	
Mucolipidosis IV	252650	Autosomal recessive	*MCOLN1*, 19p13.3–p13.2 [98–100]	TRPML1 (mucolipin-1, MLN1)	580 aa; 6 TM	Cation channel [123–126]	Na^+, K^+, Ca^{2+}; Fe^{2+}; H^+?	Mouse KO [101], *Drosophila* [121], *C. elegans* (cup-5) [112,113]	
Mucopolysaccharidosis Type IIIC (Sanfilippo syndrome C)	252930	Autosomal recessive	*HGSNAT*, 8p11.1 [6,7]	HGSNAT (TMEM76)	663 aa; 11 TM	Acetyl-transferase [75]	Alpha-glucosamine residues of heparan sulphate (lumen) + acetyl-CoA (cytosol)	None	
Niemann–Pick type C	257220	Autosomal recessive	*NPC1*, 18q11–q12 [162]	NPC1	1278 aa; 11 TM	Unknown (binds sterols) [163, 164]	Unknown	Mouse C57BLKS/J *spm* and BALB/c npc^{nih} lines [165], cat [166], *Drosophila* [167], *C. elegans* [168]	*S. cerevisiae* [169]
Danon disease	300257	X-linked dominant	*LAMP2*, Xq24 [141]	LAMP2 (LAMPB, LGP110)	410 aa; 1 TM	Lysosome fusion and motility [151], Chaperone-mediated autophagy [148]	N.A.	Mouse KO [143]	

Abbreviations: aa, amino acids; KI, knock-in; KO, knock-out; N.A., not applicable.
[a] Some helices partially span the membrane.

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