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Autophagy contributes to lysosomal storage disorders

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Degradation in the lysosome/vacuole is not the final step of autophagy. In particular, for starvation-induced autophagy it is necessary to release the breakdown products back into the cytosol. However, some researchers ignore this last step and simply refer to the endpoint of autophagy as degradation, or perhaps even cargo delivery. In many cases this is not a serious issue; however, the analysis of autophagy's role in certain diseases makes clear that this can be a significant error.

Lysosomal storage disorders, as indicated by their name, involve defects that are associated with the accumulation of substrates/macromolecules within the lysosome (**Table 1**). An important question is, how does such an accumulation contribute to the disease, and in particular, what is the relationship with autophagy? Accelerated autophagy could result in an increase in cargo delivery that exceeds the degradative capacity of the organelle, but the same phenotype could be the result of defective flux. As one example, consider Niemann-Pick type C (NPC) disease.[1,2] In patients or mouse models of NPC, unesterified cholesterol accumulates within the lysosome due to a defect in the NPC1 or NPC2 protein; these proteins are involved in transporting cholesterol out of the lysosome and into the endoplasmic reticulum and Golgi complex. This accumulation has at least two consequences that result in increased macroautophagy. First, the cholesterol trafficking defect increases the levels of BECN1, which binds to the class III phosphatidylinositol 3-kinase that induces macroautophagy. Subsequently, the increased BECN1 expression initiates a vicious cycle of promoting cholesterol accumulation and autophagosome formation; at least a part of the lysosomal cholesterol is delivered via macroautophagy, resulting in further induction of BECN1 and additional macroautophagy with yet more cholesterol accumulation. Second, prominent lysosomal accumulation of cholesterol interferes with autophagosome-lysosome fusion, which influences autophagic flux. Accordingly, *npc*$^{-/-}$ cells accumulate autophagosomes. The accumulated cholesterol may in turn result in a defect in autophagic cargo breakdown, and diminished levels of macromolecules such as amino acids being returned to the cytosol. A critical point is that treatment of NPC cannot be affected by the upregulation of macroautophagy, even though there is an overall block or delay in autophagic flux.

Phenotypes associated with the accumulation of material within the lysosome can also be seen in some cases of the neurological disorders Charcot-Marie-Tooth Type 4J (CMT4J) disease and amyotrophic lateral sclerosis (ALS). Mutations in *FIG4*, which encodes a PtdIns(3,5)P_2 5-phosphatase, result in decreased levels of the corresponding phosphoinositide (although this is a counterintuitive effect, it may reflect a tight coupling of synthesis and degradation; FIG4 is in a complex with the PtdIns3P 5-kinase FAB1). *fig4* mutant mice and fibroblasts from CMT4J patients display elevated levels of autophagosomes.[3] Furthermore, *fig4*$^{-/-}$ mice display an increase in LC3-II and SQSTM1/p62, but no upregulation of macroautophagy, suggesting a defect in autophagic flux. One role of PtdIns(3,5)P_2 in mammalian cells may be to facilitate recycling of the autolysosome membrane; this could result in the accumulation of autophagosomes as an indirect effect. It is also possible that PtdIns(3,5)P_2 is needed for fusion of autophagosomes/amphisomes with lysosomes. As with NPC, the overall defect in autophagic flux may result in a further increase in macroautophagy as the cell futilely attempts to compensate for the decrease in recycled macromolecules. Thus, attempts to treat this disease simply by upregulating autophagy are not likely to be effective. Conversely, increasing the activity of PtdIns 3-kinase (thus generating more substrate) or PtdIns3P 5-kinase may ameliorate the effects of these diseases.

These are just two examples of the importance of defining the precise nature of the autophagy-associated defect in particular diseases, and of remembering that autophagic flux involves not just the delivery of cargo to the lysosome, but also its breakdown and clearance. For further information on lysosomal storage disorders we recommend that you read the review article by Ballabio et al., in this issue of the journal.

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Table 1. Lysosomal storage disorders

Disease	Defective protein	Major storage materials
Sphingolipidoses		
Gaucher disease	GBA/acid β-glucosidase	Glucosylceramide
Fabry disease	GLA/α-galactosidase A	Globotriaosylceramide
GM1 gangliosidosis	GLB1/β-galactosidase	GM1 ganglioside
Niemann-Pick type C disease	NPC1 or NPC2	Cholesterol and sphingolipids
Mucopolysaccharidoses (MPS)		
MPS IIIA (Sanfilippo syndrome)	SGSH/N-sulfoglucosamine sulfohydrolase	Heparan sulfate
MPS VI (Maroteaux–Lamy syndrome)	ARSB/arylsulfatase B	Dermatan sulfate
Multiple sulfatase deficiency	SUMF1/sulfatase modifying factor 1	Sulfatide and glycosaminoglycans
Mucolipidoses (ML)		
ML II (I-cell disease)	GNPTAB/N-acetylglucosamine-1-phosphate transferase	Glycosaminoglycans and lipids
ML III	GNPTAB/N-acetylglucosamine-1-phosphate transferase	Glycosaminoglycans and lipids
ML IV	MCOLN1/mucolipin 1	Glycosaminoglycans and lipids
Glycogen storage disease		
Pompe disease (glycogen storage disease type II)	GAA/acid α-glucosidase	Glycogen
Danon disease	LAMP2	Glycogen and cytoplasmic debris
Neuronal ceroid lipofuscinoses (CLN)		
Batten disease (JNCL)	CLN3/battenin	Subunit c of mitochondrial ATP synthase
CLN 10	CTSD/cathepsin D	Granular osmiophilic deposits

This table shows examples of lysosomal storage diseases that are accompanied by accumulation of autophagic vesicles.

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