

Nanoparticle-Mediated Therapeutic Application for Lysosomal Function

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Nanomaterials serve as carriers for transporting conventional drugs or proteins through lysosomes to various cellular targets. The basic function of lysosomes is to trigger degradation of proteins and lipids. Understanding of lysosomal functions is essential for enhancing the efficacy of nanoparticles-mediated therapy and reducing the malfunctions of cellular metabolism. The lysosomal function is modulated by the movement of ions through various ion channels.

nanoparticles

nanomaterials

lysosome

ion channels

nanodrugs

1. Lysosomal Target of Nanoparticles (NPs) and Modulation of NPs for Lysosomal Function

1.1. pH Alteration

The primary function of the lysosome is the degradation of proteins and lipids ^{[1][2]}. The regulation of lysosomal pH has been linked to various cellular functions including the degradation of intracellular compartments. For its cellular functions, lysosomal lumen has to be maintained at an acidic pH ^[3]. Degradation of proteins, which is a crucial function of the lysosome, is carried out by more than 60 kinds of lysosomal hydrolases ^[4], and these hydrolases are optimized for the highly acidic environment of lysosomes (between pH 4.5 and 5.0) ^{[4][5]}. The lysosome as a cellular digestive system eliminates the garbage materials from autophagy and phagocytosis ^{[6][7][8]}. Thus, destabilization of lysosomal pH thorough alkalization leads to cellular toxicity and even causes lysosomal storage disease (LSD) ^{[9][10][11]}. The application of NPs can mediate various cellular functions by modulating lysosomal pH. Gold NPs (AuNPs) are known to reduce lysosomal activity by alkalization of the lysosomal lumen ^[11]. This reaction triggers oxidative stress, mitochondrial damage, and decreases cell migration/invasion ^[11]. In particular, 50-nm sized AuNPs induce autophagosomal accumulation of LC3 and block p62 degradation ^[12]. Silver NPs (AgNPs) also suppress autophagic responses by decreasing transcription factor EB (TFEB) protein expression, which is followed by lysosomal alkalization ^[13]. In addition, rare earth oxide NPs (REONPs)-mediated alkalization induces the activation of interleukin-1 β IL-1 β by an inflammasome ^[14].

1.2. Cell Viability

The lysosome consists of a typical single phospholipid bilayer to control important cellular functions ^{[15][16]}. The lysosomal membrane acts as the connector to contact other compartments such as autophagosome ^{[17][18]},

mitochondria [19], and endoplasmic reticulum (ER) [20]. On the lysosomal membrane, numerous proteins play important roles such as the mammalian target of rapamycin complex 1 (mTORC1) (nutrient sensing) [21], V-ATPase (Vacuolar type of H⁺-ATPase) (pH homeostasis) [22], and ion channels/transporters [23]. In addition, deficiency of several lysosomal membrane proteins trigger various diseases such as the Danon disease (lysosome associated membrane proteins, LAMP-2) [24], malignant infantile osteopetrosis (the chloride channel 7, CLC-7) [25], and actin myoclonus-renal failure syndrome (lysosomal integral membrane protein-2) [26]. Damaged lysosome mediates lysosomal membrane permeabilization (LMP), which contributes to cell death [27][28] and induces several diseases such as LSD and other neurodegenerative disease [29][30][31].

1.3. Protein Activity and Expression

Various lysosomal functions are mediated by more than 200 integral lysosomal membrane proteins [4], including (1) the mechanistic target of mTORC1, which is activated by nutrient starvation [28][32], and acts as a negative regulator of autophagy [28][33], and (2) LAMPs, which protect the lysosomal membrane against lysosomal hydrolases not to degrade [34]. NPs induce an inhibitory effect on the mTORC1 pathway to activate autophagy: AgNPs (decreases lysosomal protease activities) [35], Zinc oxide (ZnO) NPs (induces macrophage cell death) [36], and REONPs (induces lysosomal imbalance by TFEB nucleus translocation) [37]. ZnO NPs induce an aberrant expression pattern and de-glycosylation of LAMP-2 by ZnO-induced reactive oxygen species (ROS), which trigger cell death in lung epithelial cells [38]. Additionally, NPs modulate lysosomal motility [39]. Lysosome movement reveals two directions: toward the peripheral cytoplasm (anterograde) [40][41] and juxtannuclear region (retrograde) [42]. To carry out autophagic flux, lysosomes have to move to the juxtannuclear region [22][32], and the dynein complex is the motor protein for retrograde transport [43]. Treatment with carbon nanotubes decreases the expression of synaptosomal-associated protein (SNAP), which is a regulating factor of dynein [44] that blocks retrograde transport and, thus, the autophagic pathway [39]. Taken together, the lysosomal pathways of NPs and occupied proteins may mediate numerous functions. Thus, careful and more extensive consideration of lysosomal-associated NPs needs to be done.

1.4. Accumulation of NPs

Toxic cellular components, such as cytoplasmic macromolecules, damaged or misfolded proteins, and other worn-out organelles, are removed by lysosomes to maintain metabolic homeostasis [3]. Thus, the degradation role of lysosomes is essential for carrying out cellular homeostasis [45] including lipid catabolism [46], cell growth [47], and neurotransmission [48]. However, several NPs interrupt lysosomal degradation and deposit the lysosomal compartment in the cytoplasm. Exposure to AgNPs and copper oxide (CuO) NPs can induce agglomeration of lysosomes and subsequent cellular damage, which leads to cell death in human lung alveolar epithelial cells [49] and human umbilical vein endothelial cells [50]. In addition, NPs can accumulate in lysosomes. SiO₂NPs and PNPs impair cell viability and induce lysosomal swelling, which is followed by their accumulation in lysosomes and triggers lysosomal dysfunction and apoptosis [51][52].

2. Regulation of Lysosomal pH and Its Physiological Function

The lysosomal pH gradient is generated and maintained by movement of hydrogen ions (H^+) into the lysosomes through the action of vacuolar-type ATPases (V-ATPases) [53], which is supplemented further by movement of other ions [5]. Thus, for effective and continuous movement of H^+ into the lysosome, an accompanying counter-ion movement is necessary [5].

The lysosomal V-ATPases consists of two domains: V_1 domain, which hydrolyses ATP, and the V_0 domain, which translocates H^+ ions across the lysosomal membrane [54]. The catalytic domain V_1 , drives a rotary H^+ transport motor by hydrolyzing ATP with translocation of H^+ [55][56]. In this case, the V-ATPase rotor is operated in only one direction with an irreversible ATP hydrolysis due to the movement of H^+ from cytosol to the lysosomal lumen [5]. The continuous V-ATPase-mediated H^+ pumping generates a positive charge in the lysosomal lumen, which inhibits any further movement of H^+ [57]. To dissipate this membrane potential, other ions have to be transferred in the opposite direction, and this process is referred to as the counterion flux [5][57]. Counter ion movement is suggested as both entering anions and exiting cations through the lysosomal lumen [5]. One important counter ionic candidate is chloride, transferred by CLC-7, as attenuation of CLC-7 leads to lysosomal dysfunction such as LSD and osteopetrosis [25][58]. Another candidate counter ion is K^+ , transferred by TMEM175. Its mutation induces neuronal degeneration and LSD [59]. The R740S mutant osteoclasts, mutated in the V-ATPase $\alpha 3$ subunit, possess a higher lysosomal pH, and shows altered mTORC expression (increase in basal protein level and decrease of gene expression) and activity, which, in turn, plays a key role in cell proliferation [51][60]. Additionally, acidification of lysosomes can induce macrophages to secrete *N*-acetyl- β -D-glucosaminidase through lysosomal exocytosis [61][62], which includes absorption of cytochrome c in rat kidney during renal metabolism [63], and transport of cystine, the product of protein degradation by cathepsin, from lysosomes to cytosol [64]. Thus, alteration of lysosomal pH can be like a commander's order to modulate the cellular life cycle.

3. Lysosome-Associated Ion Channels for Lysosomal Function

The lysosomal function is modulated by the ion movement and subsequent pH regulation. This movement is accomplished through various ion channels (**Figure 1, Table 1**).

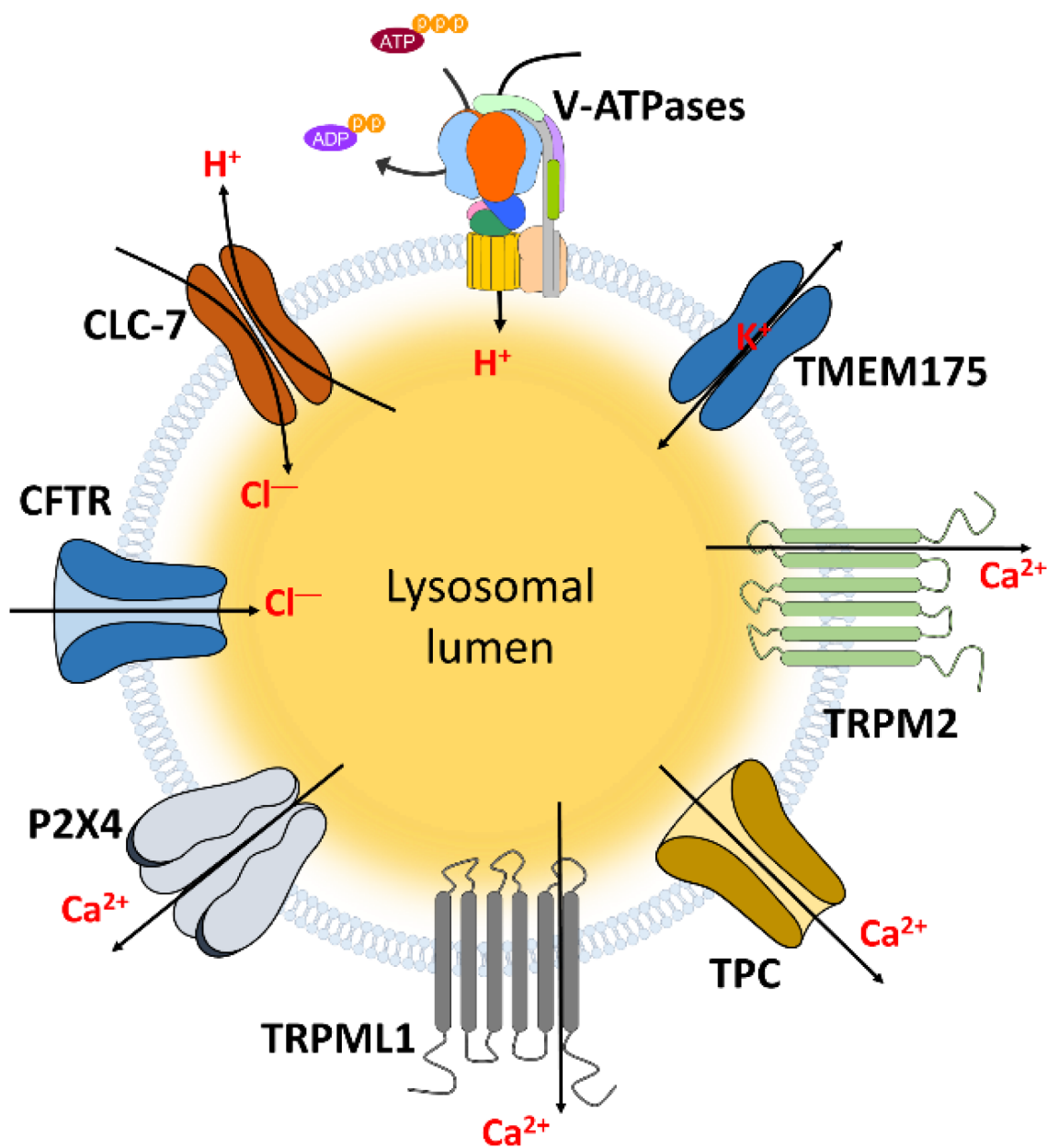


Figure 1. The channels localized in lysosomal membrane to transport ions. These channels and transporters can regulate lysosomal and cellular functions through transporting and maintaining hydrogen, chloride, Ca²⁺, and potassium which indicated in **Table 1**.

Table 1. The relationship between lysosomal ion channels and cellular functions.

Channels	Mechanisms and Related Diseases	Ref.
CLC-3	Promotion of lysosomal acidification	[65][66]
CLC-6	LSD in CLC-6 mutated neuronal cells	[67]

Channels	Mechanisms and Related Diseases	Ref.
CLC-7	Maintenance of acidic pH of lysosomes	[68][69]
	Decrease of dentinogenesis and dental bone formation in CLC-7 deficient mice	[70][71]
	Degradation of $\text{fA}\beta$ which drives AD	[72][73]
	Osteopetrosis in CLC-7 mutation	[74][75][76][77]
	LSD and neurodegeneration in CLC-7-deficient mice	[58][75]
CFTR	Support lysosomal acidification	[78]
	Decrease of bacteria killing function and phago-lysosomal fusion in macrophage	[79]
	Induce DC maturation and migration	[80]
TRPM2	Increase of actin remodeling	[81]
	Increase of pancreatic β cell apoptosis	[82]
	Increase LMP, NLRP3 inflammasome, and mitochondrial fission on the plasma membrane	[83][84]
TRPML1	Maintenance of acidic pH of lysosomes	[85]
	Increase of large particle phagocytosis, bone remodeling, gastric acid	[86][87][88][89]

Channels	Mechanisms and Related Diseases	Ref.
TMEM175	secretion, and myocytes apoptosis	
	Stomach hypertrophy, hypergastrinemia, LSD, mucopolidosis, NPC, and AD in TRPML1 deficiency	[86][90][91][92][93] [94][95][96]
	Support lysosomal Ca ²⁺ signaling and pH regulation	[97]
	Related in LSD	[98]
	Related in autophagy, cancer cell migration, and cellular pigmentation	[99][100][101]
TPC	Related in Parkinson's disease	[102][103]
	Promotion of endo-lysosomal fusion	[104][105]
P2X4		
	Related in liver fibrogenesis	[106]

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5. Clinical Application and Limitation of Nanomaterials

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Related Cellular Function	NPs	Details	Reference
pH alteration (alkalization of lysosome)	AuNPs	Increase of oxidative stress, mitochondrial damage, and decrease cell migration/invasion	[11]
		Accumulation of LC3 and block p62 degradation	[12]
	AgNPs	Decrease of TFEB protein expression	[13]
Cell viability (cell death)	REONPs	Activation of IL-1 β inflammasome	[14]
	PNPs	Decrease of autophagic flux	[111]
		Decrease of cathepsin release	[112]
	SiO ₂ NPs	Increase of membrane damage and NLRP inflammasome	[38][113]

Related Cellular Function	NPs	Details	Reference
Protein activity and expression	TiO ₂ NPs	Increase of membrane damage	[114]
	Gd ₂ O ₃ NPs	Increase of membrane damage and necrosis	[115]
	AgNPs	Decrease of lysosomal protease activities	[35]
	REONPs	Induce lysosomal imbalance by inhibiting mTORC1 pathway	[37]
	ZnO NPs	Increase of macrophage cell death by inhibiting mTORC1 pathway	[36]
Accumulation of NPs		Deglycosylation of LAMP-2	[38]
	Carbon nanotube	Decrease of SNAP	[44]
	CuO NPs	Subsequent cellular damage leading to cell death by agglomeration of lysosomes	[49][50]
	SiO ₂ NPs, PNPs	Induce lysosomal swelling leading to apoptosis	[51][52]

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