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Lysosomal TRPML1 Channel: Implications in Cardiovascular and Kidney Diseases

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Abstract

Lysosomal ion channels mediate ion flux from lysosomes and regulate membrane potential across the lysosomal membrane, which are essential for lysosome biogenesis, nutrient sensing, lysosome trafficking, lysosome enzyme activity, and cell membrane repair. As a cation channel, the transient receptor potential mucolipin 1 (TRPML1) channel is mainly expressed on lysosomes and late endosomes. Recently, the normal function of TRPML1 channels has been demonstrated to be important for the maintenance of cardiovascular and renal glomerular homeostasis and thereby involved in the pathogenesis of some cardiovascular and kidney diseases. In arterial myocytes, it has been found that Nicotinic Acid Adenine Dinucleotide Phosphate (NAADP), an intracellular second messenger, can induce Ca^{2+} release through the lysosomal TRPML1 channel, leading to a global Ca^{2+} release response from the sarcoplasmic reticulum (SR). In podocytes, it has been demonstrated that lysosomal TRPML1 channels control lysosome trafficking and exosome release, which contribute to the maintenance of podocyte functional integrity. The defect or functional deficiency of lysosomal TRPML1 channels has been shown to critically contribute to the initiation and development of some chronic degeneration or diseases in the cardiovascular system or kidneys. Here we briefly summarize the current evidence demonstrating the regulation of lysosomal TRPML1 channel activity and related signaling mechanisms. We also provide some insights into the canonical and non-canonical roles of TRPML1 channel dysfunction as a potential pathogenic mechanism for certain cardiovascular and kidney diseases and associated therapeutic strategies.

Keywords

Lysosome; TRPML1 channel; NAADP; Autophagy; Exosomes; Atherosclerosis; Chronic kidney disease

13.1 Introduction

Transient receptor potential mucolipin 1 (TRPML1) channel is a cation channel expressed in late endosomes and lysosomes [1–4]. As a member of the TRPML family of ion channels, TRPML1 is coded by the gene MCOLN1. TRPML1 channel was identified

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in a search for genesis of mucolipidosis type IV (MLIV), one of lysosomal storage diseases [5, 6]. The major symptoms of MLIV include psychomotor retardation and visual impairment [7], which are associated with the defect of lysosome trafficking and lysosomal accumulation of lipofuscin and other macromolecules including phospholipids, gangliosides, and mucopolysaccharides [8, 9]. In this chapter, we will describe the common characteristics of lysosomal TRPML1 channel and summarize the regulatory mechanisms of TRPML1 channel and related cellular activities mediated by TRPML1 channels and their regulation. We will also present some recent findings regarding the pathogenic role of lysosomal TRPML1 channel deficiency or dysregulation in cardiovascular and glomerular diseases.

13.2 Characteristics of Lysosomal TRPML1 Channels

13.2.1 Subcellular Localization of Mammalian TRPML1 Channels

As a lysosomal transmembrane protein, TRPML1 channel has two di-leucine motifs for its trafficking to lysosome [2–4]. Deletion of these di-leucine motifs may induce the accumulation of TRPML1 channel in the plasma membrane [2–4]. Also, the expression of a dominant-negative variant of dynamin was found to induce the accumulation of TRPML1 channel in the plasma membrane through abrogation of clathrin-mediated endocytosis [3]. These findings indicate that TRPML1 channel may traffic from the plasma membrane to the lysosome. However, there are evidences showing the direct delivery of TRPML1 channel to the lysosome from the trans-Golgi without intermediate translocation to the plasma membrane [4, 10]. Interestingly, overactivation of TRPML1 channel may also result in its traffic from lysosomes to the plasma membrane. For example, elevated Ca^{2+} release through TRPML1 channel due to gene mutation enhanced lysosomal exocytosis and consequent translocation of TRPML1 channel to plasma membrane [11]. In Drosophila cells, activation of the mechanistic target of rapamycin complex-1 (mTORC1) also led to the elevated level of TRPML1 channel in the plasma membrane [12]. Moreover, three mammalian TRPMLs including TRPML1, 2, and 3 are capable of forming heteromultimers [3, 13–15], and the difference in biophysical properties and regulatory mechanisms between homomultimers and heteromultimers may enhance the functional diversity of these proteins [13].

13.2.2 Biophysical Properties of TRPML1 Channels

Various sensations and ligands participate in the regulation of TRP channel activity [16]. TRPMLs are relatively small proteins consisting of <600 amino acids, and the expectation of their molecular sizes is approximately 56–65 kDa. The different sizes of TRPML1 channel may range from 36 to 75 kDa due to cleavage and other modifications in various native cells [6, 17]. A similar topology to other TRP channels was found in TRPML1 channel. The ion channel is formed at the center of the canonical homotetrameric assembly which is formed by TRPML1 channels. Each subunit is composed of six transmembrane helices (S1–S6), two-pore helices (PH1 and PH2), and a luminal domain [18]. The characteristics of TRPML1 channel include a TRP channel-homologous region and an internal pore region for the passage of Ca^{2+} and Na^{+}. Also, TRPML1 channel is characterized with the location of both NH_2 and COOH terminal chains in cytosol. The activity of TRPML1 as a nonspecific cation channel is permeant to Ca^{2+} and H^{+} and thereby controlled by lysosomal luminal and cytosolic Ca^{2+} and H^{+} concentrations [19, 20].

The activity of TRPML1 reaches the maximum at pH 4.6, which is nearby the mean value of lysosomal lumen pH of mammalian cells [21, 22]. In Drosophila, the optimal pH for maximal activation of TRPML1 channel is pH 5.2, consistent with the mean luminal pH of insect lysosomes [23].

As channels insensitive to voltage but gated by ligands, TRPMLs have been extensively studied regarding their ion selectivity. For example, it has been demonstrated that human TRPML1 ion selectivity is $Ba^{2+}>Mn^{2+}>Fe^{2+}=Ca^{2+}=Mg^{2+-} > Ni^{2+} = Co^{2+} = Cd^{2+} > Zn^{2+} \gg Cu^{2+}$. In the presence of 30–105 mM Fe^{2+}, its pS is 32–40 at pH 4.6 [21, 22]. Nevertheless, most of previous studies characterized lysosome TRPML1 channel in cell lines transfected with TRPML1 genes. Recently, by lipid bilayer reconstitution and single lysosome patch clamping, we have demonstrated the normal function of the TRPML1 channel in lysosomes isolated from rat hepatocytes, coronary arterial myocytes, human fibroblasts, and murine podocytes [24–27]. The native TRPML1 channels can be activated by Nicotinic acid adenine dinucleotide phosphate (NAADP). In addition, the opening of TRPML channel can be blocked by its specific TRPML1 channel blockers, TRPML1 siRNA, and neutralized antibody against TRPML1 channel.

Many studies have elucidated the physiological relevance of the Ca^{2+} conductivity of TRPML1 channel to the regulation of lysosome maturation, autophagic flux, lysosomal exocytosis, and Ca^{2+} signaling-related cellular activities [20, 28]. However, the functional significance of the conductance of TRPML1 channel to other ions beyond Ca^{2+} has not yet been well clarified. Based on the conductance of the TRMPL1 channel to Fe^{2+}, it has been assumed that TRPML1 may contribute to the hematological and degenerative abnormality in MLIV via regulation of the cellular homeostasis of Fe^{2+} [11, 21]. Clearly, more studies are needed to explore the physiological relevance of the conductance of TRPML1 channel to other ions beyond Ca^{2+}.

13.3 Agonists and Blockers of TRPML1 Channel

13.3.1 NAADP

As a metabolite of $NADP^+$, NAADP has been reported to induce Ca^{2+} release from sea urchin egg microsomes [29–31]. Since then, it was demonstrated that NAADP is produced by the soluble protein Aplysia ADP-ribosylcyclase and its membrane-bound homologs, CD38 and CD157 [32–35]. These enzymes can exchange the terminal nicotinamide group of the $NADP^+$ with nicotinic acid to produce NAADP through a base-exchange reaction, which has been found in various cells and tissues, such as smooth muscle cells, pancreatic acinar cells, human T lymphocytes, sea urchin eggs, and rat brain [36–39]. In our recent studies, we have demonstrated that CD38 and its cytosolic isoforms have been found to produce NAADP in mouse coronary artery in response to death receptor activation, endothelin, and oxidant stimulation [40, 41].

Our previous studies on redox signaling and lipid raft-associated transmembrane signaling mechanisms [40, 42, 43] indicate that some agonists or stimuli may generate an acid microenvironment in vascular cells. For example, both FasL and ET-1 have been found to preferably stimulate NAADP production in vascular smooth muscle cells (VSMCs) [41, 44],

which may be associated with their ability to generate a local acidic microenvironment at the cell membrane, facilitating a base exchange reaction via CD38. The formation of this local acidic environment might be attributed to lipid raft clustering if agonist receptors are linked to lipid rafts. Previous studies have shown that the clustering of membrane lipid rafts may induce the activation of CD38 [42, 45–47]. The agonist-induced membrane raft clustering is usually initiated by lysosome fusion to the cell membrane, which translocates critical proteins to the cell membrane for raft clustering such as acid sphingomyelinase (ASM) and lysosomal vacuolar H^+-ATPase. A local acidic environment is provided by lysosomal vacuolar H^+-ATPase, which maintains the normal function of translocated ASM to produce ceramide for the construction of lipid raft platforms [43]. Such membrane microenvironment of acidic pH generated and maintained by vacuolar H^+-ATPase is critical for the production of NAADP by CD38 within lipid raft platforms.

When we searched for the molecular target of NAADP action in lysosomes, reconstitution, and characterization of NAADP-sensitive Ca^{2+} channel from lysosome of rat liver was first done in our laboratory using lipid bilayer. In 2007, we have demonstrated a reconstituted Ca^{2+} channel with all the biophysical and pharmacological features of TRPML1 in liver lysosomes [26]. In bovine coronary arterial muscle cells, we further characterized this TRPML1 channel using lysosome preparations by the constitution in the lipid bilayer. In arterial muscle preparation, we have demonstrated that the reconstituted lysosomal channel is also a voltage-dependent Ca^{2+} channel [25]. It was found that NAADP activates TRPML1 channel reconstituted from the liver and coronary arterial muscle lysosome preparations in a concentration-dependent manner. In addition, high concentrations of NAADP may result in self-desensitization of TRPML1 channel. In the bilayer preparations containing coronary arterial muscle lysosomal channels, pretreatment with a subthreshold concentration of NAADP substantially attenuated the activity of these channels in response to higher concentrations of NAADP, which indicated the self-desensitization property of these lysosomal channels. This self-desensitization property of lysosomal ion channels has also been shown in the actions of NAADP as a Ca^{2+}-releasing second messenger in other cells such as sea urchin egg fractions or intact egg cells [48–50].

Pharmacologically, these reconstituted lysosomal channels in both liver and coronary arterial lysosomes were blocked by commonly used antagonists of TRPML1 channels such as NAADP receptor antagonist PPADS, sodium channel antagonist amiloride, and dihydropyridine derivatives nifedipine and verapamil [26, 51]. Using gene silencing, deprivation of TRPML1 protein, and interference of its channel pore formation, NAADP was shown to induce Ca^{2+} release from the lysosomal store via TRPML1 channel-mediated Ca^{2+} release [25]. More recently, lysosomal TRPML1 channels have been reported to regulate local compartmental Ca^{2+} which importantly controls lysosome function such as trafficking or intracellular signaling [27].

13.3.2 Phosphoinositides

As a low-abundance lysosome-specific phosphoinositide [52–55], phosphatidylinositol-3,5-bisphosphate (PI(3,5)P2) can be generated from PI(3)P through PIKfyve/Fab1, a PI 5-kinase that locates in the lysosome of both yeast and mammalian cells [54, 56–58]. Several

associated proteins, such as Fig4, Vac14, and Vac7, can enhance the activity of PIKfyve/Fab1 [53–55, 59]. Also, the myotubularin (MTM/MTMR)-family of PI-3 phosphatase can metabolize PI (3,5)P2 into PI(5)P [54, 58, 60]. A variety of neurodegenerative diseases can be induced by gene mutations of PI(3,5)P2-metabolizing enzymes and their regulators, such as Charcot–Marie–Tooth disease and amyotrophic lateral sclerosis [53, 54, 61]. Recently, it has been found that PI(3,5)P2 activates lysosome-localized TRPML1 channels specifically and potently [22, 62–64]. Enlarged lysosomes and vacuoles and deficient lysosome trafficking were found in both PI(3,5)P2-deficient cells and TRPML1-deficient cells [53–55, 59]. In PI(3,5)P2-deficient mouse fibroblasts, the enlargement of vacuole can be inhibited by overexpression of TRPML1 [62].

On the contrary, PI(4,5)P2 has been found to potently inhibit the opening of TRPML1 channel [64]. Overexpression and plasma membrane translocation of 5-phosphatase can potentiate whole-cell TRPML1 currents through degradation of PI(4,5)P2. Thus, inhibition by PI(4,5)P2 may serve as a mechanism to inactivate lysosome-operating TRPML1 channels upon plasma membrane insertion. It has been known that different PIP2 products may have different effects on TRPML1 channel activity, such as the inhibitory effects of the plasma membrane-specific phosphoinositides PI(4,5)P2, PI(3,4,5) P3, and PI(3,4)P2 and the stimulatory effect of lysosome-specific PI(3,5)P2. This suggests that the activity of TRPML1 channel is economically and efficiently regulated by these compartment-specific phosphoinositides.

In a recent study, the structure of mouse TRPML1 channel has been uncovered by single-particle cryo-electron microscopy after its embedding in nanodiscs [65]. Its structure indicates that the coupling of ligand binding to pore opening may depend on the binding of PIP2 to the N-terminus of the channel and the helix-turn-helix extension between S2 and S3. Under the closed condition, two equally distributed conformations of the S4–S5 linker have been observed, which implies that S4–S5 linker may mediate the gating of TRPML1 channel by PIP2.

13.3.3 Synthetic Agonists and Blockers

Xu and his associates developed an elegant approach using patch-clamp techniques and recorded Fe^{2+} and Ca^{2+} channel activity directly from the lysosome membrane in different cell types with TRPML1 transgene. They have discovered that TRPML1 is a proton-impermeable and inwardly rectifying cation channel, which is dually permeable to Ca^{2+} and Fe^{2+}/Mn^{2+} [11, 21, 62]. More recently, the same group used a genetically encoded Ca^{2+} indicator (GCaMP3) attached directly to TRPML1 to directly measure Ca^{2+} release from lysosomes via TRP-ML1 [66], which further confirms the nature of TRPML1 as a lysosomal Ca^{2+} release channel. These studies have demonstrated that all three members of the mammalian TRPML subfamily, TRPML1–3, are activated by mucolipin synthetic agonist 1 (ML-SA1). More recently, it has been revealed that ML-SA1 may have therapeutic potential against some lysosome storage diseases, in which TRPML1 expression and function may be diminished. For example, the defect in lysosomal function was found in cells from patients with Niemann–Pick (NP) disease, one of the lysosome storage diseases that resulted in alterations in Ca^{2+} and Fe^{2+} homoeostasis, defects in lipid trafficking, and impairments in

autophagosome–lysosome fusion and/or lysosome reformation [67, 68]. Similar pathological changes can also be observed in MLIV, which led to a broad examination of TRPML1 channel function in cells with NP disease type A and type C (NPA and NPC) mutations and cells lack of NPC1 gene ($NPC1^{-/-}$ cells). It was found that the activity of TRPML1 channel was remarkably inhibited by NPA and NPC mutations or NPC1 gene deletion, suggesting that reduction of TRPML1 channel activity is a consequence of NP disease [67]. Mechanically, the activity of the TRPML1 channel was directly inhibited by sphingomyelin, which is abnormally accumulated in lysosomes in all NP disease cells. Moreover, the lysosomal function in $NPC1^{-/-}$ cells was recovered by enhancement of TRPML1 expression or activation of TRPML1 by ML-SA1 [67]. In a recent study, it has been reported that Duchenne muscular dystrophy in mouse models can be ameliorated by ML-SA5 through activation of TRPML1 channel [69]. Therefore, the pharmacological intervention of the TRPML1 channel by synthetic agonist may be an effective strategy to rescue lysosomal function in various lysosomal storage disorders. However, the mechanism mediating the action of ML-SA1 on TRPML1 remains unclear. Before the discovery of ML-SAs, previous studies showed that SF-22 and SF-51 have stimulatory effects on TRPML1 channel [67, 70]. It has been found that ML-SA1 induced more potent activation of TRPML1 channel compared to SF-51 [67]. As an mTOR inhibitor, rapamycin has been reported to have direct activating action on TRPML1 channels [71]. All these activators can be used to study TRPML1 channel activity and its physiological and pathological relevance in different cells or tissues.

It was found that amiloride, ruthenium red, nifedipine, 2APB, and SKF 96365 as commonly used cation channel and/or Ca^{2+} channel blockers failed to inhibit TRPML1 or TRPML3. Verapamil and La^{3+}, however, have been demonstrated to block both TRPML1 channel and TRPML3 channel [25, 72, 73]. ML-SI1, a novel selective TRPML1 inhibitor, has also been found to block the opening of TRPML1 channel, leading to inhibition of particle uptake and lysosomal exocytosis in bone marrow-derived macrophages [74]. More recently, ML-SI3 and ML-SI6 have been reported to inhibit TRPML1 channel activity [69] in a more specific manner, which can be used as tool drugs for studies on these lysosomal channels.

13.4 Associated Proteins of TRPML1 Channel

13.4.1 ALG-2

A recent study has shown that TRPML1 channel interacts with apoptosis-linked gene 2 (ALG-2) in a Ca^{2+}-dependent manner, which impacts endolysosomal vesicle trafficking [75]. As a Ca^{2+}-binding protein, ALG-2 belongs to the penta-EF-hand protein family [76]. The conformation of ALG-2 is changed in response to Ca^{2+}, which enhances its affinities to its binding partners [76–78]. It has been found that ALG-2 binds to the amino-terminal tail of TRPML1 channel in a Ca^{2+}-dependent manner. Furthermore, mutation of the ALG-2-binding domain in TRPML1 channel may result in the disarrangement of its distribution and function, suggesting that TRPML1 channel activity is regulated by ALG-2. More recently, there is evidence showing that lysosomal distribution is controlled by ALG-2 as a Ca^{2+} effector of the TRPML1 channel [79]. The overexpression of ALG-2 in fibroblasts resulted in a dramatic perinuclear distribution of lysosomes, which was abolished

by inhibition of TRPML1 channel. On the other hand, activation of TRPML1 channel with ML-SA1 increased the amount of ALG-2 on the lysosomal membrane. Importantly, ALG-2 pulled down dynamitin, a dynactin complex component, in coimmunoprecipitation assays in a Ca^{2+}-independent manner [79]. We have also found that NAADP induces Ca^{2+} release through TRPML1 channels via ALG-2 (data not published). In mouse coronary arterial myocytes, ALG-2 was found abundantly expressed in the cytosol. Using confocal microscopy, FasL and ET-1, two well-known NAADP stimulators were found to increase the colocalization coefficient of ALG-2-GFP with TRPML1-RFP in these arterial myocytes. Immunoprecipitation with anti-ALG-2 antibody, the interaction of ALG-2 with TRPML1 channel in the lysosome, was confirmed, which was enhanced upon NAADP stimulation. In addition, recombinant ALG-2 protein binding with NAADP as receptors was significantly reduced by NAADP, and NAADP-induced lysosomal Ca^{2+} release was blocked by ALG-2 siRNA. These results demonstrate that ALG-2 indeed directly binds to NAADP and thereby may mediate the action of NAADP-induced lysosomal Ca^{2+} release via lysosomal TRPML1 channels.

13.4.2 Hsc70

The chaperone-mediated autophagy (CMA) selectively determines the recycle of soluble cytosolic proteins [80]. The selectivity of CMA depends on the recognition of a targeting motif in soluble cytosolic proteins by a chaperone, which is essential for the transportation of these proteins to the lysosomal surface [80]. As a constitutively expressed member of the 70-kDa family of chaperones, the heat shock cognate protein of 70 kDa (Hsc70) recognizes the substrate of CMA in the cytoplasm [81]. Recently, it has been demonstrated that Hsc70 interacts with TRPML1 channel in yeast two-hybrid and co-immunoprecipitation experiments [82]. In starvation studies, a working model has been suggested that lysosomal TRPML1 activity upon starvation may release Ca^{2+} to promote lysosomal Hsc70 recruitment. This TRMPL1–Hsc70 interaction enhances CMA and shifts metabolism from an anabolic toward a catabolic, thereby exerting nutrient-liberating action [79]. In macrophages of MLIV patients, the defect of CMA has been found in response to serum withdrawal, indicating that the interaction between TRPML1 channel and Hsc70 is essential for CMA. Furthermore, the reduction of lysosome-associated membrane protein type 2A is associated with the elevation of oxidized proteins in MLIV fibroblasts. All these results tell us that the delivery of substrates to the lysosomal surface depends on TRPML1 channels as a docking site for Hsc70 during CMA [82].

13.4.3 LAPTM

More recently, a novel interaction between the TRPML1 channel and the members of the lysosome-associated protein transmembrane (LAPTM) family has been identified [83]. In ARPE-19 cells, LAPTM4a, LAPTM4b, and LAPTM5 showed very high degrees of colocalization with the TRPML1 channel in late endosomes and lysosomes [83]. Functionally, overexpression of LAPTM4b caused enlargement of late endosomes and lysosomes, which can be prevented by overexpression of TRPML1 channels [83]. In HeLa cells, dysfunction of LAPTM4 resulted in a phenotype similar to lysosomal storage disease found in MLIV patients [83]. Correspondingly, a previous study has shown that expressions of LAPTM4a and LAPTM5 in MLIV cells increased threefold and sevenfold, respectively

[84]. This changes the compensation attempted by MLIV cells due to the lack of LAPTM activity. In summary, LAPTM–TRPML1 interaction is important for the normal function of lysosomes and that the defect of this interaction is implicated in the pathogenesis of MLIV.

13.5 Regulatory Mechanisms of TRPML1 Channel Activity

13.5.1 Cathepsin B

The lysosomal proteases contribute to antimicrobial host defense against infection. As lysosomal proteases, cathepsins provide antimicrobial host defense against infection through degradation of intracellular bacteria within lysosomes. The reduction of capacity to kill bacteria has been reported in macrophages lacking cathepsin D during pneumococcal infection [85]. Also, the susceptibility to infections by *Porphyromonas gingivalis* and *Staphylococcus aureus* was amplified by the knockout of the cathepsin E gene [86]. Moreover, cathepsin L has been reported to inhibit the infection of *Mycoplasma pulmonis* [87]. On the contrary, there is evidence indicating that the activity of cathepsin B may contribute to bacterial infection.

TRPML1 channel may be inactivated after cleavage by lysosomal proteases. Recently, it has been reported that cathepsin B mediates the critical or final cleavage of TRPML1 channel [88]. The cleavage of the TRPML1 channel constitutes a regulatory mechanism to limit the duration of TRPML1 channel activity, which is important to the maintenance of lysosomal ionic homeostasis. In a recent study, the elevation of resistance to Francisella novicida, a cytosolic bacterial pathogen, has been found in mice and macrophages lacking cathepsin B activity [89]. Mechanically, defect in cathepsin B function inhibited mTOR activity and prevented cleavage of TRPML1 channel. In response to these changes, transcription of lysosomal and autophagy genes increased lysosomal biogenesis and enhanced the activity of autophagy initiation kinase ULK1 for bacteria clearance, which depended on transcription factor EB (TFEB). Interestingly, it has been found that inhibition of TRPML1 channel expression leads to the leak of lysosomal protease cathepsin B into the cytoplasm [90]. The leak of cathepsin B is associated with apoptosis, which can be prevented by pharmacological inhibition of cathepsin B activity. These findings indicate that modulation of cathepsin B activity may be a potential therapeutic strategy to enhance host immunity against certain bacterial infections. Also, cathepsin B might be a therapeutic target for the treatment of debilitating lysosome storage diseases.

13.5.2 TOR–TFEB Signaling Pathway

In autophagy, unwanted cellular components are digested for the generation of catabolites that are used for housekeeping biosynthesis processes in response to nutrient starvation. A recent study has reported that the activity of TRPML1 is potently and rapidly increased upon nutrient starvation [91]. In this study, starvation-induced boost of lysosomal degradation capability was completely abolished by pharmacological inhibition or genetic deletion of TRPML1, indicating the essential role of TRPML1 channel in the lysosomal adaptation to nutrient starvation [91]. Similar to nutrient starvation, the complete suppression of mTORC1 function remarkably increased TRPML1 channel-mediated Ca^{2+} release [91]. Mechanically, TFEB nuclear translocation is triggered after nutrient starvation or complete inhibition

of mTORC1 [91, 92]. The expression of TRPML1 channel is upregulated by nuclear translocation or overexpression of TFEB [91, 93]. Furthermore, TOR as a nutrient-sensitive protein kinase has been found to directly target and inactivate the TRPML1 channel through phosphorylation [94]. The mutations of phosphorylation sites of the TRPML1 channel blocked the inhibition of TRPML1 channel activity by TOR [94].

13.5.3 Phosphorylation

The function of protein is importantly regulated by post-translational modifications. Phosphorylation and dephosphorylation events play vital roles in the regulation of the activity of many TRP channels. Serine, threonine, and tyrosine residues are targets of TRP phosphorylation, which is catalyzed by various kinases, including tyrosine kinase, PKA (protein kinase A), PKC (protein kinase C), PKG (protein kinase G), and CaMKII (Ca^{2+}/calmodulin-dependent protein kinase II) [95]. In a recent study, it has been demonstrated that the activity of TRPML1 channel is modulated by phosphorylation [96]. FSK-induced activation of PKA enhanced phosphorylation of TRPML1 channel, leading to inhibition of TRPML1 channel activity. On the contrary, the activity of the TRPML1 channel was remarkably amplified after the inhibition of PKA by H89. These results indicate that PKA may be involved in the regulation of lysosomal function through modulation of TRPML1 channel activity.

13.5.4 Regulation of TRPML1 Channel Activity by Sphingolipids

Ceramide is the central core in sphingolipid metabolism and plays an essential role in normal cell and tissue homeostasis and in the development of numerous diseases [97, 98]. The hydrolysis of sphingomyelin by acid sphingomyelinase (ASM) leads to the production of ceramide, which preferentially occurs in lysosomes or other acidic vesicles. Lysosomal acid ceramidase (AC) metabolizes ceramide into sphingosine which can be phosphorylated by sphingosine kinase for the generation of sphingosine-1-phosphate (S1P) [99, 100]. Recent studies have shown that sphingomyelin accumulation inhibits lysosomal TRPML1 channel-mediated Ca^{2+} release and thereby leads to impaired lysosome trafficking and lysosomal storage disease as shown in Niemann–Pick disease [67, 101]. On the contrary, lysosomal Ca^{2+} release through the TRPML1 channel and associated lysosome trafficking are enhanced by sphingosine. More recently, we have demonstrated that sphingolipid metabolism by AC regulates TRPML1 channel activity [24]. The defect in AC function may block TRPML1 channel, leading to lysosome dysfunction and increased exosome release from podocytes [24]. These findings suggest that sphingolipid signaling plays a pivotal role in the regulation of lysosomal TRPML1 channel activity and thereby determines Ca^{2+}-dependent lysosome trafficking and fusion to multivesicular bodies (MVBs) that govern exosome release. However, it remains unknown how sphingolipids alter the activity of TRPML1 channel. Further study on this regulatory mechanism would be beneficial to our understanding of the regulation of TRPML1 channel under both physiological and pathological conditions.

13.5.5 Redox Regulation of TRPML1 Channel Activity

A variety of active oxygen-containing compounds are generally called reactive oxygen species (ROS), including hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), and free

radical (superoxide and hydroxyl radicals) [102]. Biomacromolecules involved in different cellular activities can be damaged by ROS [103]. On the contrary, ROS is essential for the redox signaling cascade in many crucial cellular processes [104]. A simultaneous balance of ROS is maintained by cellular oxidation and antioxidation. Cellular damage can be induced by oxidative stress when oxidation exceeds antioxidation [105]. There is increasing evidence showing that the boost of autophagy may be attributed to the production of ROS, which is a vital defensive mechanism against cellular stress [106, 107]. Under conditions such as ischemia, hypoxia, and nutrient starvation, autophagy may be induced by mitochondrial ROS [108–110]. Nevertheless, autophagosome accumulation was observed after induction of autophagy by ROS [111–113], which indicated that lysosome-dependent autophagosome degradation may be interfered. Therefore, the actions of ROS on the molecules controlling lysosomal functions, such as TRPML1 channel, need to be studied.

A recent study has focused on the regulation of TRPML1 channel by ROS or oxidants in some cell lines [113]. The actions of a variety of commonly used oxidants on the TRPML1 channel have been tested in this study. It was found that chloramine-T, a nonselective strong oxidant, activated TRPML1 channel with a potency comparable to those of PI(3,5)P2 and ML-SA1. Furthermore, several other commonly used oxidants, including NaOCl, H_2O_2, *N*-chlorosuccinimide, t-butyl hydroperoxide (TBHP), and thimerosal, have been found to activate TRPML1 channel less potently. Cysteine-modifying oxidants such as DTNP and DTNB24, however, failed to induce the opening of TRPML1 channel. Similarly, SNAP, a NO-donor, and 4-HNE25, a reactive lipid peroxidation intermediate, did not affect the activity of TRPML1 channel. However, among these different oxidants, only H_2O_2 mimics the mitochondrial ROS while the dose of H_2O_2 in this study was too high (10 mM). Furthermore, various forms of ROS or oxidants that produced effects on TRPML1 channel activity vary a lot in this study, which made the conclusion of this study uncertain. At least, ROS from different resources and ROS at different levels may play diverse roles in the regulation of TRPML1 channel activity. Functionally, carbonyl cyanide *m*-chlorophenylhydrazone (CCCP), a mitochondrial respiration inhibitor commonly used to induce ROS production, was found to induce autophagic clearance of damaged mitochondria through activation of TRPML1 channel [113]. Conversely, another previous study has shown that CCCP induced autophagosome accumulation and apoptosis through activation of TRPML1 channel [114]. Recently, we have tested whether ROS affects TRPML1 channel activity in murine podocytes (data not published). It was found that pretreatment of H_2O_2 (100 μM) totally blocked the opening of TRPML1 channel induced by ML-SA1. Moreover, pretreatment with homocysteine (Hcy), an inducer of endogenous ROS production [115], remarkably attenuated Ca^{2+} release through the TRPML1 channel induced by ML-SA1. These results indicate that ROS may act as a danger factor by inhibiting TRPML1 channel activity under pathological conditions, such as hyperhomocysteinemia (hHcy). In this regard, it has been found that many compounds, including *N*-acetylcysteine, Ferulic acid, and Trehalose, reduce ROS and enhance autophagy simultaneously [116–118]. These findings may support the possibility that ROS inhibits lysosome function through blockade of TRPML1 channels.

Interestingly, the TRPML1 channel has been found to mediate the removal of ROS [113, 119]. In RPE1 (retinal pigmented epithelial 1) cells, inhibition of TRPML1 channel

expression remarkably increased lipid peroxidation, which indicated the elevation of ROS production [119]. Also, depolarization and morphological changes in mitochondria were induced by siRNA of TRPML1 channel in these cells [119]. In another study, repolarization of mitochondrial membrane potential after CCCP treatment was much slower in MLIV cells compared with wild-type cells [113]. The basal level of ROS in MLIV fibroblasts was much more than the basal level of ROS in wild-type cells. Constitutive elevation of ROS and chronic inhibition of TRPML1 were observed in ML-IV cells and NPC cells [67]. Furthermore, blockade of TRPML1 channel by ML-SI4 markedly enhanced CCCP-induced ROS production in HeLa cells [113]. Collectively, these findings unveil that inhibition of TRPML1 channels by ROS and clearance of ROS by TRPML1 channel may form a balance under normal conditions, and this balance may be broken by pathological stimuli.

In addition to the controversy of the role of ROS in TRPML1 channel regulation, the mechanisms by which ROS control TRPML1 channel activity are under exploration. For example, previous studies have demonstrated that ROS enhanced the activity of Cathepsin B while having no effects on the expression of Cathepsin B [120, 121]. The enhancement of Cathepsin B activity by ROS may lead to inhibition of TRPML1 channel activity through increased cleavage of TRPML1 channels. Furthermore, it has been found that sanguinarine (SNG), a naturally occurring benzophenanthridine alkaloid, can induce ROS production and apoptotic cell death in human leukemic cells [122]. In addition, ceramide accumulation due to activation of ASM and inhibition of AC may be the mechanism mediating SNG-induced ROS production and apoptosis in human leukemic cells [122]. In MDA-MB-231 cells, the combination of C6-ceramide and DM-102, an AC inhibitor, was reported to enhance ROS production remarkably [123]. These findings indicate the complex interactions in the regulatory system of TRPML1 channel activity. For our better understanding of the impact of ROS on TRPML1 channels, further studies are imperative on this regulatory pathway. Regulatory mechanisms of TRPML1 channel activity are summarized in Fig. 13.1.

13.6 Functions of TRPML1 Channels in Health and Diseases

13.6.1 Lysosomal pH Control

The regulatory effect of the TRPML1 channel on lysosomal pH remains debatable. It has been reported that TRPML1 channel may mediate the release of H^+ from the lysosomal lumen [88, 124–126]. The dysfunction of TRPML1 channel may lower the lysosomal pH. Also, it was found that elevation of the lysosomal pH by Nigericin or Chloroquine attenuated the lysosomal storage in MLIV cells [125]. However, another study found that treatment with Nigericin or Chloroquine had no significant effect on the lysosomal storage in MLIV cells [127]. Moreover, there is evidence showing that TRPML1 channel is not permeable to H^+ [21, 73]. Taken together, the exact role of TRPML1 channel in the regulation of lysosomal pH remains unclear and further studies are necessary.

13.6.2 Fusion and Fission of Cell Membrane

Previous studies have reported that TRPML1 channel activity is essential to cellular activities associated with vesicular trafficking, such as autophagy, lysosomal exocytosis, and the formation of early endosomes [20]. All these cellular functions require the fusion

and fission of the membrane. In this regard, defect in TRPML1 channel or PI(3,5)P2 has been found to block lysosome-to-Golgi retrograde trafficking, a process requiring membrane fission [2, 8, 54–58, 128–131]. Also, it has been reported that membrane-fusion processes including exocytosis and fusion of lysosome and autophagosome are dependent on the TRPML1 channel and PI(3,5) P2-metabolizing enzymes [11, 54, 58, 132, 133]. Protein complexes are recruited by the local elevation of PI(3,5)P2, leading to the generation of membrane curvature and consequent membrane fusion and fission [58]. Also, the activity of TRPML1 can be enhanced by the local elevation of PI(3,5)P2, leading to the increase in juxtaorganellar Ca^{2+} that affects SNARE proteins and lipid bilayer fusion [58, 134] via binding to putative Ca^{2+} sensor proteins such as ALG-2 [75] and Synaptotagmin/CaM [135]. These findings have shown that the normal function of the TRPML1 channel is essential for membrane fission and fusion.

13.6.3 Autophagy

Lysosome as a primary digestive organelle is responsible for the degradation of membrane proteins, membrane polysaccharides, complex lipids, endocytosed membranes, and autophagocytosed organelles. In recent studies, it has been found that a number of neurodegenerative disorders may be attributed to impaired lysosomal function and consequent autophagic deficiency [136–139]. As a lysosomal storage disorder, MLIV is featured by severe ophthalmological and neurological abnormalities caused by defective lysosomal transport of membrane components. The accumulation of enlarged vacuoles containing phospholipids, sphingolipids, and acid mucopolysaccharides was observed in fibroblasts obtained from MLIV patients [140–143], suggesting that the transport of protein and lipids is dependent on TRPML1 channel. It has been reported that the fusion of lysosome and autophagosome is inhibited in fibroblasts of MLIV patients [144]. TRPML1 channel was found to mediate the fusion of lysosome and autophagosome [20, 144, 145]. Also, Ca^{2+} released through the TRPML1 channel was found to activate calcineurin (Cn) which is responsible for the dephosphorylation of TFEB. Then, dephosphorylated TFEB translocated to the nucleus to initiate the transcription of lysosomal and autophagic genes [146, 147]. Thus, TRPML1 and TFEB form a positive feedback loop in which activation of TRPML1 or TFEB enhances the action of the other factor [147, 148]. Recently, it has been found that TRPML1 contributes to autophagosome biogenesis, which is attributed to the induction of the Beclin1/VPS34 autophagic complex, the activation of calcium/calmodulin-dependent protein kinase kinase β (CaMKKβ), the boost of AMP-activated protein kinase (AMPK), and the generation of phosphatidylinositol 3-phosphate (PI3P) [149]. These findings suggest that the TRPML1 channel plays an important role in the regulation of autophagy and the control of cellular metabolism.

13.6.4 Lysosomal Exocytosis

Previous studies have shown that the TRPML1 channel mediates the exocytosis of lysosomes [150–152]. Also, the elevation of TRPML1 channel activity due to gene mutations may induce constitutive lysosomal exocytosis, leading to remarkable translocation of TRPML1 channels to the plasma membrane [11]. Furthermore, it has been found that the TRPML1 channel contributes to the construction of tubular extensions on the cell surface as a consequence of lysosomal exocytosis [153]. In mouse macrophages, the

transport of major histocompatibility complex II to the plasma membrane and the escape of endocytosed macromolecules from the lysosomes requires the normal function of the TRPML1 channel [130]. Moreover, lysosomal exocytosis is promoted by upregulation of TRPML1 channel expression due to overexpression of TFEB [148, 154], confirming the critical role of the TRPML1 channel in lysosomal exocytosis. A recent study has shown that the TRPML1 channel is required for focal exocytosis of lysosomes to the site of phagosome formation at the plasma membrane, indicating the contribution of the TRPML1 channel to phagocytosis [74]. Loss or inhibition of TRPML1 channel function decreased the phagocytosis of senescent and apoptotic cell corpses [74]. In the Drosophila MLIV model, lack of TRPML1 channel resulted in deficient phagocytic uptake of apoptotic neurons, leading to the precipitous onset of neurodegeneration [126].

13.6.5 Mitochondrial Function

There is increasing evidence suggesting the functional crosstalk between lysosome and mitochondrion [155, 156]. In unbiased protein interaction studies, the physical interaction between the TRPML1 channel and several mitochondrial proteins was observed [157]. Also, aberrations in mitochondrial function, morphology, and Ca^{2+} buffering capacity were found in cells lacking the TRPML1 channel [158]. Furthermore, genetic deletion of TRPML1 channel induced neuronal cell loss in the brains of Drosophila adults, which was attributed to dysfunction of the mitochondrion, accumulation of mitochondria with dissipated electrochemical membrane potentials, diminished autophagic clearance of damaged mitochondria, and elevation of ROS [126]. In a recent study, loss of mitochondrial membrane potential and the enhancement of ROS production were observed in mammalian cells lacking the TRPML1 channel [119].

13.6.6 Triggering of Large Ca^{2+} Release from Sarcoplasmic Reticulum

As a ubiquitous Ca^{2+} messenger, NAADP acts as one of the most potent intracellular Ca^{2+} mobilizing molecules [35, 159–161]. The Ca^{2+} mobilizing action of NAADP is even stronger than that induced by commonly known Ca^{2+} mobilizing second messengers IP3 and cADPR [30, 31]. It has been reported that the ryanodine receptor (RyR) is a possible target for the action of NAADP in mobilizing Ca^{2+} from intracellular stores [162–167]. However, other studies agreed more with the findings that in sea urchin eggs, there is an acidic compartment related to lysosomes [168]. In recent studies, NAADP has been demonstrated to first activate Ca^{2+} bursts as a triggering mechanism and then lead to global Ca^{2+} mobilization through IP3Rs and RyRs in the sarcoplasmic reticulum (SR), a so-called two-pool mechanism. It is assumed that the NAADP-sensitive Ca^{2+} store or acidic Ca^{2+} store is responsible for a localized signal, where the latter triggers Ca^{2+}-induced Ca^{2+} release (CICR) to cause global Ca^{2+} increases through RyRs or IP3Rs on the SR [41, 169, 170]. Recent studies in our laboratory have shown that NAADP may not directly activate RyRs on the SR in VSMCs [25, 26, 44]. Instead, we have demonstrated that NAADP induces Ca^{2+} release through the lysosomal TRPML1 channel, which leads to large Ca^{2+} release through RyRs on the SR [25].

Although the two-pool mechanism is attractive in its interpretation of a two-phase Ca^{2+} release induced by NAADP, some issues remain to be addressed. For example, a long

delay of the second phase Ca^{2+} release (seconds to minutes) has been confirmed in NAADP-induced CICR [41, 171, 172], which is very different from the classical CICR reported previously [173–177]. Between lysosomal clusters and a subpopulation of SR, the lysosome–SR junction has been found to form a trigger zone, where NAADP-induced lysosomal Ca^{2+} release through the TRPML1 channel activates a global Ca^{2+} response via CICR in pulmonary VSMCs and some other cells [41, 44, 169]. In collaboration with Dr. van Breemen, who has extensive experience in characterizing plasma membrane–SR and mitochondria–SR junctions in smooth muscle cells under resting and contracting condition [178, 179], we performed electron microscopy and found that there are lysosome–SR junctions around 30–80 nm in VSMCs, which are relatively large compared to plasma membrane–SR and mitochondria–SR junctions. However, these Lysosome–SR junctions are rather heterogeneous within arterial myocytes (Fig. 13.2a). Based on the dimensional characteristics of the lysosome–SR junction obtained by electron microscopy, we built a three-dimensional reconstruction of a typical lysosome–SR junction, including lysosome (green), SR (yellow), TRPML1 channel (blue), SERCA2 pumps (red), and Ca^{2+} (white) (Fig. 13.2b). Given the great mobility of lysosomes in cytosol, lysosome–SR junction possibly depends on lysosomal movement toward SR [25]. It has been proposed that lysosomal aggregation around SR contributes to the global Ca^{2+} release following small Ca^{2+} bursts from lysosomes. Although lysosomal Ca^{2+} release through TRPML1 channel may not be enough to induce global Ca^{2+} release from the SR, it may be enough to drive lysosomal movement toward SR. When these clustered lysosomes work together, global Ca^{2+} release from the SR is activated [25]. This interaction of lysosome and SR was also proposed later by Zhu et al. in pulmonary VSMCs [172]. Furthermore, we have demonstrated that NAADP stimulates lysosome trafficking through its Ca^{2+} mobilizing action [27].

Recently, the two-pool mechanism has been found to regulate vasoconstriction. In this regard, Evans and associates first reported that intracellular dialysis of NAADP induced spatially restricted “bursts” of Ca^{2+} release, leading to global Ca^{2+} wave and contraction in pulmonary artery smooth muscle cells [180]. Depletion of SR Ca^{2+} stores with thapsigargin and inhibition of RyRs with ryanodine both blocked the global Ca^{2+} waves by NAADP [180]. In VSMCs, this two-pool mechanism has been demonstrated to function in response to different agonists such as FasL and ET-1 or by delivery of NAADP into the cells [41, 44]. In coronary arteries, we also found that ET-1-induced NAADP production mobilized intracellular Ca^{2+}, which depends on the normal function of the lysosome [44]. The lysosome function inhibitor bafilomycin A1 and NAADP antagonist PPADS substantially blocked ET-1-induced maximal coronary arterial constriction. These results indicate that NAADP-induced Ca^{2+} release through lysosomal TRPML1 channel may contribute to ET-1-induced Ca^{2+} mobilization in CASMCs and consequent vasoconstriction of coronary arteries [44]. More recently, we further demonstrated that FasL increased the production of NAADP but failed to induce vasoconstriction in coronary arterial preparation. However, IP3-producing agonist U46619-induced coronary arterial contraction was significantly enhanced by FasL, suggesting that arterial contraction may be sensitized by elevation of NAADP production [41]. CICR in VSMCs is shown in Fig. 13.3.

13.6.7 Podocyte Differentiation and Podocytopathy

According to previous studies, the differentiation and maturation of podocytes are highly dependent on normal autophagy [181–183]. Our recent studies have demonstrated that autophagic flux or autophagy maturation is importantly attributed to lysosomal function in mouse podocytes and that lysosome dysfunction may result in autophagic deficiency and consequent podocyte dedifferentiation [183, 184]. Recently, we have demonstrated that CD38 controls lysosome function and thereby regulates autophagic flux in podocytes [183]. It was found that inhibition of CD38 attenuated the fusion of lysosome and autophagosome, leading to autophagosome accumulation in podocytes. Moreover, NAADP, the product of CD38, has been shown to play an essential role in the autophagic flux in podocytes. PPADS, an antagonist of the NAADP receptor, decreased GPN-induced lysosomal Ca^{2+} release and inhibited autophagic flux in podocytes. These results indicate that NAADP-induced lysosomal Ca^{2+} release through the TRPML1 channel may contribute to autophagic flux in podocytes. Furthermore, we have demonstrated that dysfunction of CD38 enhances podocyte dedifferentiation, leading to glomerular injury and sclerosis [184]. These findings indicate that CD38–NAADP–TRPML1 signaling pathway may be a therapeutic target for podocyte dedifferentiation and glomerular diseases due to autophagic deficiency.

Previous studies have disclosed that obesity is a risk factor for chronic kidney disease (CKD) and end-stage renal disease (ESRD) [185, 186]. In adolescents with severe obesity, an early glomerular injury may be detected using urinary sphingolipid excretion as a parameter, which is proposed according to a recent clinical study reporting that urinary sphingolipid excretion occurs in adolescents with severe obesity despite the absence of microalbuminuria [187]. The elevated urinary sphingolipids include ceramides, sphingomyelin, and glycosphingolipids. In the development of obesity-induced glomerular diseases, exosomes may play an important role, given the recent discovery that ceramide-enriched exosome stimulates further damage in response to danger signals [188–190]. As one of the extracellular vesicles (EVs), the exosome is released after the fusion of MVB to the plasma membrane [191]. The involvement of exosomes in cell communication and the pathogenesis of different diseases has been extensively studied [192–194]. There is evidence that lysosomal function determines the fate of various intracellular vesicles, including phagosomes, autophagosomes, and MVBs [27, 183, 195, 196]. Recently, we have reported that lysosome trafficking and lysosome–MVB interaction in podocytes are controlled by TRPML1 channel-mediated Ca^{2+} release [72]. Dysfunction of lysosomal AC may block the TRPML1 channel. The lack of Ca^{2+} release through the TRPML1 channel may decrease lysosome–MVB interaction, leading to enhancement of exosome secretion from podocytes. Under pathological conditions, enhancement of podocyte-derived exosome release due to blockade of TRPML1 channel may contribute to podocyte injury and glomerular damage. Regulations of autophagic flux and exosome release by TRPML1 channels in podocytes are summarized in Fig. 13.4.

13.6.8 Exosome Release and Arterial Medial Calcification

The process of apatite calcium salts accumulate and deposit within the vascular wall is known as arterial calcification which has been reported to be associated with atherosclerosis, diabetes mellitus, aging, and CKD [197]. Arterial calcification is anatomically classified

into intimal and medial calcification [198]. In arterial intimal calcification, artery occlusion often occurs due to lipid accumulation, inflammation, and fibrosis, which is featured by irregularly scattered deposits in the atherosclerotic plaques [199]. In arterial medial calcification (AMC), the elevation of arterial stiffness is attributed to continuous deposition of hydroxyapatite in the absence of inflammatory cells along the internal elastic lamina [200, 201].

In recent studies, arterial SMC-derived exosomes in the vascular interstitial space have been reported to contribute to the development of arterial medial calcification [202–204]. Given the important role of the lysosomal TRPML1 channel in the regulation of exosome release [72], we hypothesized that dysfunction of the lysosomal TRPML1 channel may block lysosome trafficking and fusion to MVBs in arterial SMCs, leading to enhanced exosome release from arterial SMCs. A recent study in our laboratory has demonstrated that the normal function of lysosomal AC may be essential for the maintenance of contractile phenotype and lysosome-dependent degradation of MVBs in arterial SMCs [205]. The SMC-specific deletion of the Asah1 gene was found to result in enhanced exosome secretion, SMC phenotypic transition, and AMC. The regulatory role of AC is attributed to the action of AC-associated sphingolipids on the lysosomal TRPML1-mediated Ca^{2+} release. In arterial SMCs lack of Asah1 gene, the dysfunction of the TRPML1 channel led to reduced lysosome–MVB interaction and enhanced exosome release, which contributed to the development of AMC [205]. Furthermore, a recent study has demonstrated that phenotypic transition of arterial medial SMCs can be enhanced by deletion of Mcoln1 gene in a mouse model of AMC [206]. The deletion of the Mcoln1 gene induced an abnormality of lysosome positioning and elevation of exosome release, which contributed to the development of AMC [206]. These findings have further confirmed that the normal function of the lysosomal TRPML1 channel is essential for the maintenance of contractile phenotype and lysosome-dependent degradation of MVBs in arterial SMCs.

13.6.9 Lysosome-Mediated Autophagic Flux and Atherogenesis

Acute experiments in cells and isolated vessels have indicated that NAADP is involved in the development of hypertension and pulmonary hypertension [159]. However, so far there is no direct evidence showing that this CD38-derived second messenger is implicated in any vascular diseases. Given the diversity of cell types in the artery wall and the involvement of autophagy in different vascular cell functions, the role of autophagy in the development of atherosclerosis is complex [207–209]. It has been demonstrated that autophagy can generate either protective or detrimental effect on atherosclerosis, which is determined by the status of autophagy and the stage of atherosclerosis [210, 211]. Damaged components in the arterial wall can be cleaned up by autophagy, leading to the recovery of cells from the damage in response to atherosclerotic stimuli. Moreover, autophagosomes can engulf defective or damaged mitochondria for autophagic degradation, which inhibits proapoptotic protein release and cell apoptosis [212–214]. This autophagic flux may protect arterial cells from atherogenic injury. However, damaged lysosomes may release hydrolases, engage as part of oxidative stress, and enhance cellular damages in response to acute or persistent oxidative stress during atherosclerosis [211, 215–217]. Enhanced or reduced autophagy plays different roles in the development of atherosclerosis depending on the different

cells involved. For example, cholesterol transport out of macrophages is increased by autophagy, which may reduce foam cell formation by prevention of lipid droplet formation. Enhanced autophagic death of macrophages also attenuates foam cell formation, which may inhibit atherosclerotic injury. Autophagy contributes to the maintenance of differentiated, quiescent, and contractile phenotype of arterial SMCs, leading to the inhibition of cell proliferation and prevention of fibrosis. Nevertheless, the death of arterial SMCs may be induced by excessive autophagy, which increases the instability of atherosclerotic plaques. In endothelial cells (ECs); however, excessive activation of autophagy may induce damage of the endothelium and initiate atherogenic injury [215, 217–220]. Although these previous studies have demonstrated the complex role of augmented autophagy in atherosclerosis, the role of autophagic deficiency in the pathogenesis of atherosclerosis remains unknown.

In our recent studies, we have demonstrated that autophagic deficiency also importantly contributes to atherogenesis. In vivo, it was found that CD38 gene knockout amplified Western diet-induced autophagosome accumulation in coronary arterial media [221]. In vitro, both deletion of CD38 gene and inhibition of TRPML1 channel expression remarkably attenuated fusion of lysosome and autophagosome, leading to autophagosome accumulation in CAMs. Defects in the CD38–NAADP–TRPML1 signaling pathway promoted CAM dedifferentiation and stimulated the production of the extracellular matrix, which contributed to the development of atherosclerosis [221]. Another study has shown that CD38 is essential for the normal function of nuclear factor E2-related factor 2 (Nrf2) in CAMs [222]. The dedifferentiation of CAMs is attributed to the downregulation of Nrf2 in CD38 gene knockout CAMs [222]. As an event observed in the early stage of atherosclerosis, increased collagen I deposition in the extracellular matrix may be caused by excess formation or decreased degradation or both of collagen I in CAMs [223]. In this regard, we have demonstrated that CD38–NAADP–TRPML1 signaling pathway plays an important role in the regulation of autophagy and thereby controls collagen metabolism [195]. The collagen I deposition and arterial wall thickening in mice fed with Western diet were enhanced by CD38 gene knockout [195]. As a hallmark in the development of atherosclerosis, cholesterol accumulation in macrophages was worsened by blockade of CD38–NAADP–TRPML1 signaling pathway [224]. Compared to wild-type mice, Western diet-induced atherosclerosis and lysosomal cholesterol sequestration in macrophages were more severe in CD38 gene knockout mice [224]. Taken together, these findings have demonstrated the importance of CD38–NAADP–TRPML1 signaling pathway in the maintenance of normal function of the coronary artery. The lysosome trafficking and autophagic flux are dependent on TRPML1 channelmediated Ca^{2+} release, which is essential for the homeostasis of CAMs.

13.7 Concluding Remarks

There is increasing evidence that the lysosomal TRPML1 channel is implicated in the regulation of cardiovascular and glomerular functions and may be involved in the development of cardiovascular and glomerular diseases. TRPML1 channel-mediated lysosome Ca^{2+} bursts activate CICR that is an important regulatory mechanism of vasoconstriction. Furthermore, TRPML1 channel regulates various cellular activities, including autophagy, lysosomal exocytosis, apoptosis, lipid transportation, and exosome release. All these studies have provided innovative insights into the physiology and

Pathobiology of TRPML1 channels, which may help develop therapeutic strategies preventing the development of vascular diseases such as arterial calcification and atherosclerosis. In addition, dysfunction of TRPML1 channels has also been implicated in the development of a variety of glomerular diseases due to their induction of podocyte dysfunction and injury, resulting in glomerular sclerosis and ultimate ESRD. A deeper mechanistic investigation is of the utmost importance to understand how pathological stimuli regulate lysosomal TRPML1 channel activity, which may further promote the development of more effective therapies for the prevention or treatment of chronic degenerative cardiovascular and glomerular diseases.

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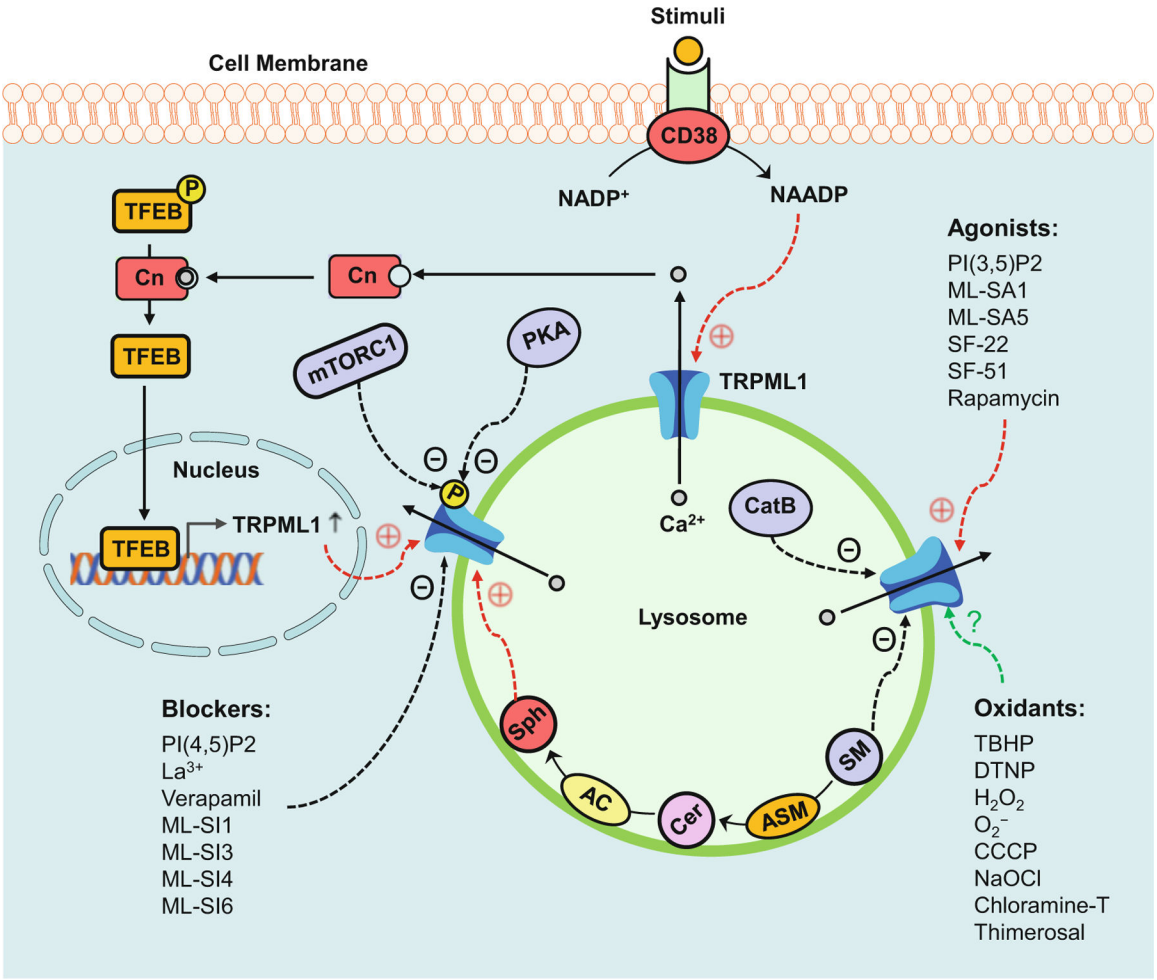

Fig. 13.1.

Regulatory mechanisms of TRPML1 channel activity. TRPML1 channel agonists such as PI(3,5)P2 and ML-SA1 may induce the opening of this channel. TRPML1 channel blockers such as PI(4,5)P2 or ML-SI1 may block this channel. In response to stimuli such as FasL and ET-1, CD38 converts $NADP^+$ to NAADP that may activate the TRPML1 channel. PKA and mTORC1 are responsible for the phosphorylation of the TRPML1 channel which may result in dysfunction of this channel. Ca^{2+} released through the TRPML1 channel activates calcineurin (Cn) which is responsible for the dephosphorylation of TFEB. Dephosphorylated TFEB translocates to the nucleus to initiate the transcription of lysosomal and autophagic genes. Sphingolipids have different effects on TRPML1 channel activity, with inhibition by sphingomyelin (SM), no effect from ceramide (Cer), and enhancement by sphingosine (Sph). Cathepsin B mediates the critical or final cleavage of TRPML1 channel which results in dysfunction of this channel. The effects of oxidants on the TRPML1 channel remain controversial

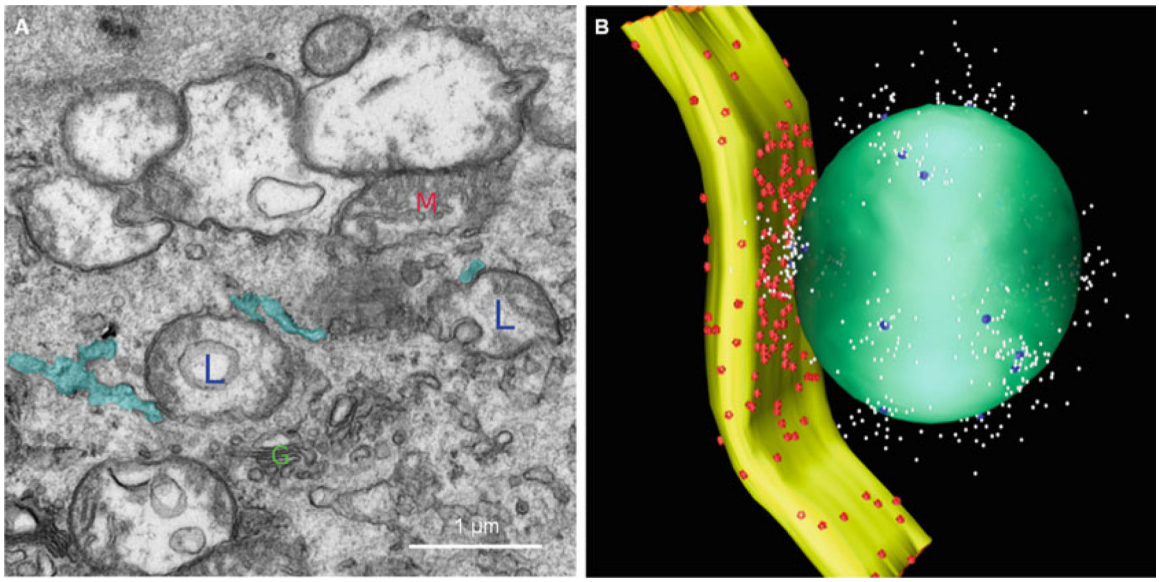

Fig. 13.2.

Lysosome–SR junction. The image obtained by electron microscopy shows the structure of the lysosome–SR junction. Lysosomes are labeled with L; SRs are labeled with blue color; the mitochondrion is labeled with M; the Golgi is labeled with G. Based on the dimensional characteristics of the lysosome–SR junction obtained by electron microscopy, we built a three-dimensional reconstruction of a typical lysosome–SR junction, including lysosome (green), SR (yellow), TRPML1 channel (blue), SERCA2 pumps (red), and Ca^{2+} (white)

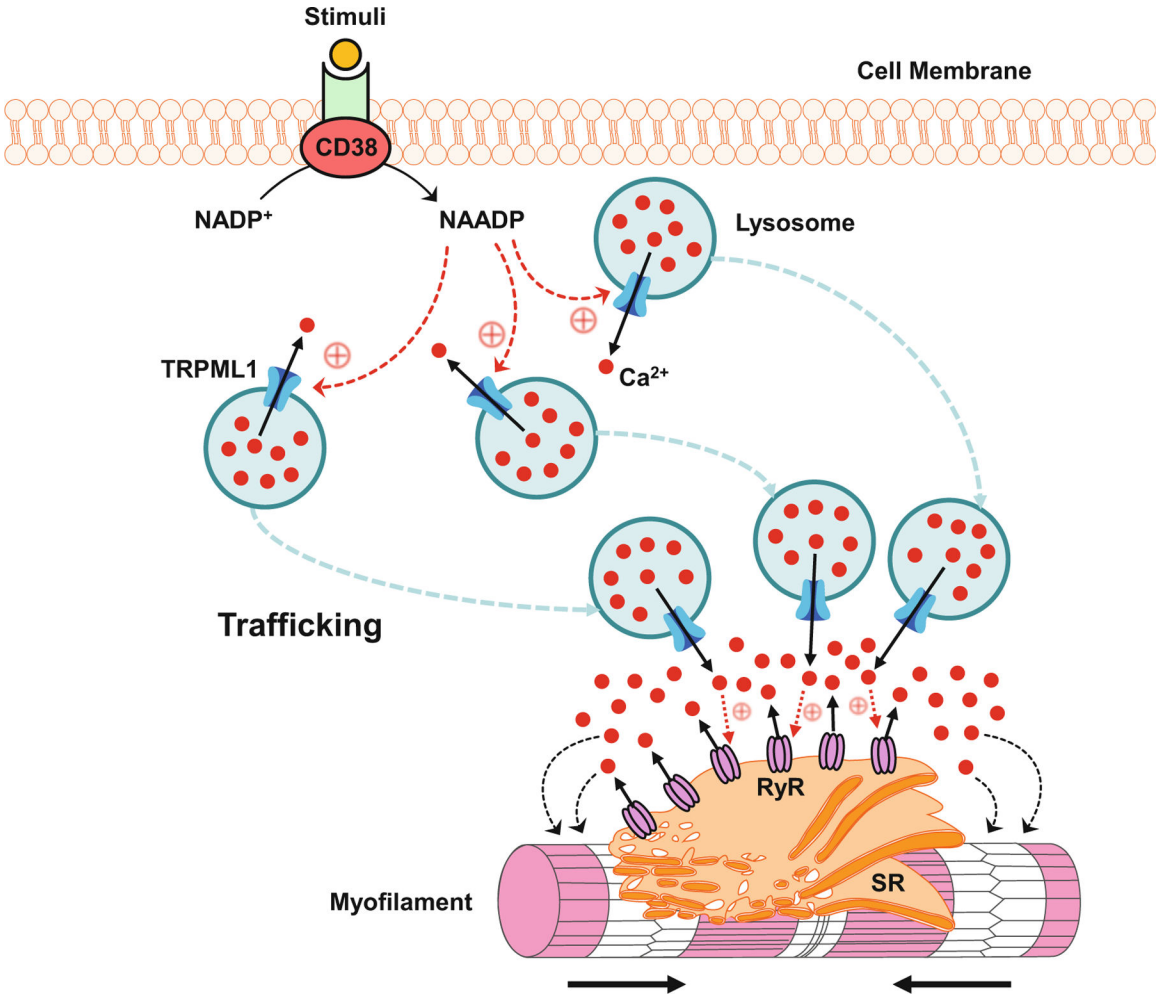

Fig. 13.3.

CICR in VSMCs. In response to stimuli such as FasL and ET-1, CD38 converts $NADP^+$ to NAADP which may activate TRPML1 channel. Ca^{2+} released through the TRPML1 channel drives lysosome trafficking toward the SR, where aggregated lysosomes further release Ca^{2+} to activate RyRs to produce large Ca^{2+} release from the SR, leading to the contraction of myofilament

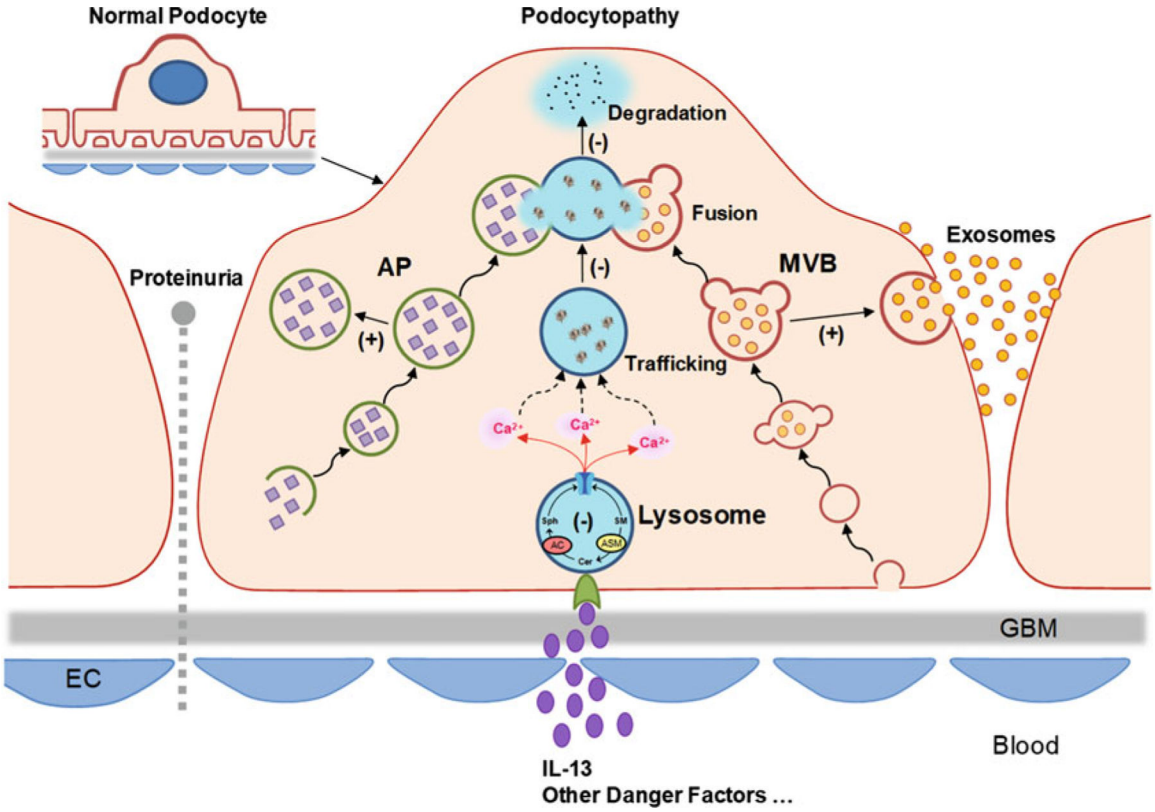

Fig. 13.4.

Regulations of autophagic flux and exosome release by TRPML1 channels in podocytes. Autophagosomes (APs) and multivesicular bodies (MVBs) can fuse with and deliver content to lysosomes for degradation, which is regulated by lysosome trafficking. This lysosome-mediated regulatory mechanism constitutively controls the fate of APs and MVBs. Sphingolipids have different effects on TRPML1 channel activity, with inhibition by sphingomyelin (SM), no effect from ceramide (Cer), and enhancement by sphingosine (Sph). Ca^{2+} released through TRPML1 channel drives lysosome trafficking to and fusion with APs or MVBs. AC deficiency or inhibition may undermine lysosome–AP and lysosome–MVB interactions, leading to accumulation of APs and increased release of exosomes, which in turn triggers or promotes podocyte phenotypic transition and podocytopathy