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Dual Roles of CD38 in Autophagy

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Abstract

CD38 is a versatile, ubiquitously expressed protein that was identified as a multifunctional enzyme. Recently, cumulating evidence has suggested that CD38 is involved in autophagy, which is an evolutionarily conserved lysosomal degradation and recycling system. Acting as a enzyme, CD38 utilizes nicotinamide adenine dinucleotide phosphate (NADP) to synthesize nicotinic acid adenine dinucleotide phosphate (NAADP), which acts as a key messenger for Ca^{2+}-mobilizing in lysosome by targeting two-pore channels (TPCs) or transient receptor potential mucolipins (TRPMLs). Multiple studies have indicated that CD38 is involved in autophagy by modulating intracellular Ca^{2+} signaling. However, the control of autophagy by CD38 signaling is the subject of two contrary views. The autophagosomes trafficking and fusion with lysosomes to form autolysosomes are crucial steps in autophagy. On the one hand, the available evidence indicates that lysosome trafficking and fusion to autophagosomes is positively modulated by CD38. On the other hand, overexpression of TPC2, which is positively modulated by CD38, was shown to promote the accumulation of autophagosomes, thus suppress autophagy. This review will reveal the interesting contrary dual roles of CD38 in autophagy, and critical insight into the molecular mechanisms of CD38 in autophagy regulation.

Keywords

CD38, Autophagy, Calcium, NAADP, Lysosome, Autophagosome

1. CD38 and Calcium Signaling

1.1. The Function and Basic Structure of CD38

CD38 is a type II membrane protein, originally identified as a cell surface differentiation marker in B lymphocytes, and later found to be expressed ubiquitously [1] [2]. In fact, CD38 is a versatile molecule with big ambitions. Although early studies revealed that CD38 serves as a differentiation antigen on cell sur-

face, multiple studies have indicated a more diverse role for CD38 in many physiological and pathological processes, including Ca^{2+} signaling, autophagy, tumorigenesis, autism spectrum disorder (ASD), richter syndrome, acquired immune deficiency syndrome (AIDS) and type II diabetes [2]-[14].

As a transmembrane protein, human CD38 is a 46-kDa glycoprotein, which consists of three conserved regions: a short N-terminal topological domain (NTD, residues 1 - 21), a single transmembrane helix domain (TMD, residues 22 - 44) and a long C-terminal catalytic domain (CCD, residues 45 - 300) (**Figure 1**). Some key amino residues in C-terminal catalytic region are responsible for nucleosidase activity of CD38. Mutations of the three residues W125F, W189G and E226G, affect the catalytic activity and subsequent calcium signaling [13]. CD38 catalyzed synthesis of cADPR, which increased intracellular Ca^{2+} and resulted in microglial activation and activation-induced cell death [14]. Moreover, CD38 contains some variations in single nucleotide that occur at specific sites in the genome, called single-nucleotide polymorphisms (SNPs), which have been used in genome-wide association studies (GWAS) as a key marker in gene mapping related to human diseases. The SNP position of CD38 at residues R140 (corresponding to rs1800561) is closely related to ASD or type II diabetes [9] [11]. Another SNP site rs6449182 at P184 is associated with richter syndrome [9] [10] [11]. Besides, the three disulfide bonds of CD38 are sponsored by cysteine residues between C160 and C173, C254 and C275, C278 and C296 [13]. The N-linked glycosylation modifications are usually occurring at four asparagine residues N100, N164, N209 and N219 [15]. These disulfide bonds and glycosylation modifications might play important roles in the topology of CD38 [4].

1.2. CD38, a Key Messager for Intracellular Ca^{2+}-Mobilizing

Generally speaking, intracellular Ca^{2+} oscillation arise either from its release
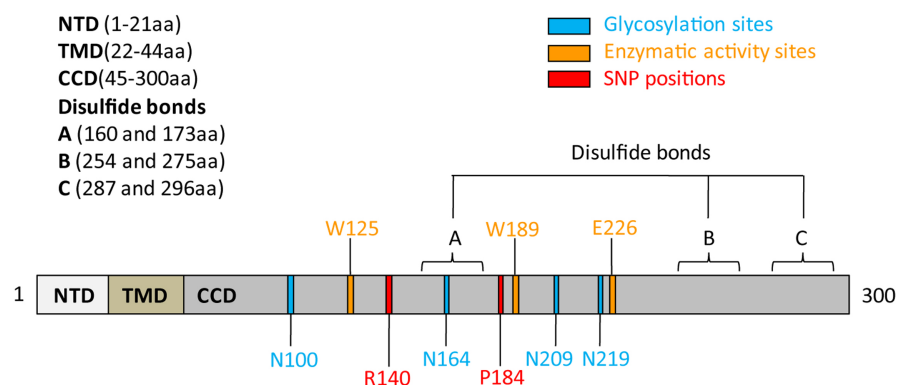

Figure 1. The structure of human CD38. Human CD38 contains three conserved domains: a short N-terminal topological domain (NTD, residues 1 - 21), a single transmembrane helix domain (TMD, residues 22 - 44) and a long C-terminal catalytic domain (CCD, residues 45 - 300). Three residues W125, W189 and E226 are responsible for nucleosidase activity of CD38. Two SNP positions occur at residues R140 and P184. The three disulfide bonds of CD38 are sponsored by cysteine residues between C160 and C173, C254 and C275, C278 and C296. The N-linked glycosylation modifications are occur at four asparagine residues N100, N164, N209 and N219.

from intracellular stores, such as endoplasmic reticulum (ER), endolysosome and mitochondria, or by modulating Ca^{2+} channels at the plasma membrane, including voltage-dependent calcium channels (VDCCs), Na^+/Ca^{2+} exchanger (NCX), plasma membrane calcium-transporting ATPases (PMCAs), cyclic nucleotide-gated ion channels (CNGCs), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and N-methyl-D-aspartate receptor (NMDAR) [2] [16].

As we known, Streb *et al.* discovered the Ca^{2+}-mobilizing activity of inositol 1,4,5-triphosphate (IP_3), which targets IP_3 receptor (IP_3R) in ER and stimulates ER-Ca^{2+} release [2] [17]. In addition to IP_3, cyclic ADP-ribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP) are also identified as important intracellular Ca^{2+} messengers, which elicit intracellular Ca^{2+} flux from either ER or endolysosome. As a multifunctional enzyme, CD38 is responsible for the synthesis of cADPR and NAADP from NAD and NADP, respectively [2] [3]. Besides, CD38 also plays a critical role in the degradation of NAADP by hydrolyzing NAADP to ADP-ribose 2'-phosphate [18]. It is known that both IP_3 and cADPR trigger Ca^{2+} release from the ER via the IP_3R and ryanodine receptors (RYR), respectively. However, the other potent Ca^{2+}-mobilizing messenger NAADP drive Ca^{2+} flux from the endolysosomal pools by targeting the two-pore channels (TPCs) or transient receptor potential mucolipin-1 (TRPML1) [3] [19] [20]. Intriguingly, the CD38/NAADP-mediated lysosome Ca^{2+} signaling have been shown to participate in the physiological regulation of cell functions or activities, such as autophagy and apoptosis [21]. Cumulating evidence has suggested that autophagosomes trafficking and fusion with lysosomes is a NAADP/Ca^{2+} signaling dependent process [22]. Thus, modulating the production of NAADP in cells by CD38 may be play important roles in lysosomal functions, especially autolysosomes formation and autophagic contents elimination.

2. Autophagy: A Brief Introduction

Autophagy, also called self-eating, a natural and evolutionarily conserved lysosomal degradation and renovation process to hydrolyze unused or dysfunctional cellular components, such as long-lived or misfold proteins and useless organelles [23]. Actually, the basal autophagy activity is essential for cell homeostasis, involving cell growth, survival, development and death. The levels of autophagy must be precisely regulated, as indicated by the fact that dysfunctional autophagy has been related to wide ranges of human diseases, such as cancer [24] [25], neurodegenerative diseases [26], myopathies [27], gastrointestinal disorders [28], heart and liver diseases [29]. The most interesting is the study about autophagy and cancer. There are dual roles of autophagy in tumorigenesis [25] [30]. On the one hand, autophagy was thought to be a tumor-suppression mechanism. In normal cells and tissues, autophagy usually acts as a tumor suppressor by autophagy-mediated recycling [30] [31]. By preventing the toxic accumulation of damaged protein and organelles, particularly mitochondria, autophagy resists oxidative stress and oncogenic signaling, which inhibits malignancy. One the

other hand, autophagy also plays tumor-promoting roles. In most contexts, cancers can induce autophagy to survive microenvironmental stress and to increase growth and aggressiveness [25] [30].

In recent years, autophagy has attracted great interest in the biological and medical sciences. Actually, there are at least three types or pathways of autophagy, including macroautophagy, microautophagy and chaperone-mediated autophagy [32]. One common hallmark of autophagy is mediated by the multiple autophagy-related (Atg) genes and their associated enzymes. The main and most common pathway, macroautophagy, usually called autophagy, is an intracellular recycling system, used primarily to mediate bulk degradation of superfluous or damaged cytosolic materials [23]. This autophagy processes include several steps: 1) induction and formation of a double membrane vesicle known as an autophagosome, 2) autophagosomes trafficking and fusion with lysosomes to form autolysosomes, and 3) degradation and recycling of autophagic contents via acidic lysosomal hydrolases (**Figure 2**).
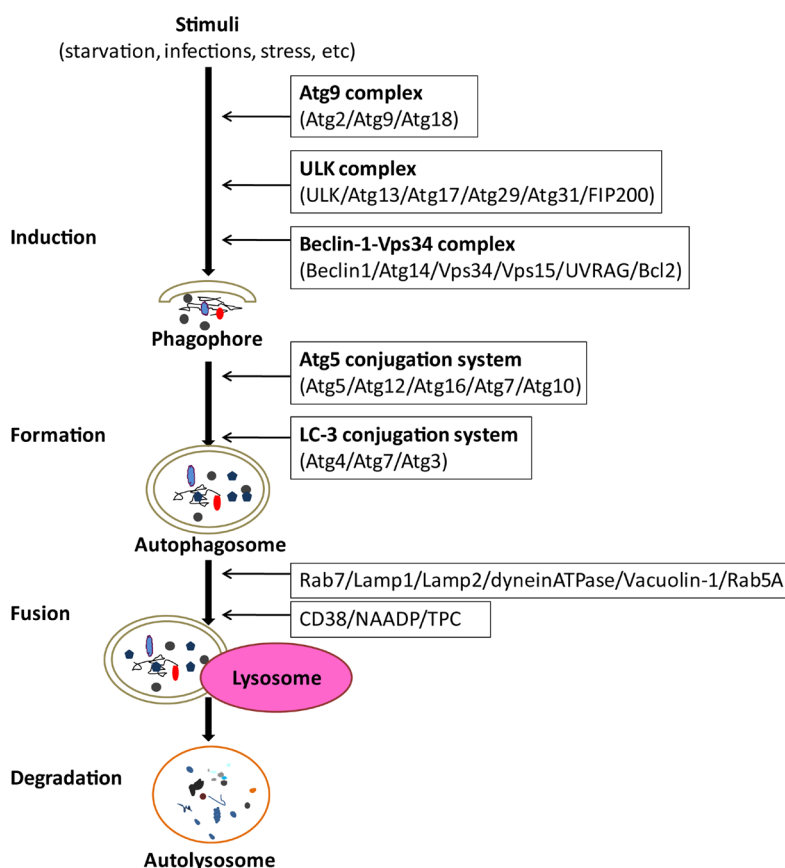

Figure 2. The overview of autophagy. The Atg9 complex, ULK complex and Beclin-1-Vps34 complex are important for induction of autophagosome. Besides, autophagosome formation also requires both LC3-II and Atg12-Atg5-Atg16L conjugation systems. The autophagosomes trafficking and fusion with lysosomes to form autolysosomes is controlled by a lot of factors, including Rab7, Rab5A, Lamp1/Lamp2, dynein ATPase, Vacuolin-1, TRPMLs and TPCs. In the breakdown step, autophagic materials or contents are hydrolyzed by lysosomal enzymes in autolysosome.

As an evolutionarily ancient response to cellular stress, cell autophagy can be evoked by a wide variety of stresses, including nutrition starvation, bacterial and viral infection, drought, salt, senescence and oxidative stress. Indeed, the autophagy process is executed by more than 30 Atg factors and associated proteins in response to stimuli. It is known that autophagy is initiated at the phagophore assembly site (PAS) in yeast [33]. Yamamoto *et al.* demonstrated that the Atg13-mediated supramolecular assembly is responsible for autophagy initiation [34]. Yao *et al.* indicated that the Atg1 complex bond to Atg9-vesicles, thus facilitating the induction of autophagy [33]. In fact, autophagosome formation is the most complicated event, which is driven by series larger molecular complexes. As illustrated in Figure 2, autophagy induction is controlled by the Unc-51-Like kinase (ULK, also called Atg1) complexes [34] [35] [36], Atg9 complexes [33] and autophagosome formation requires Beclin-1-Vps34 complexes [23] [37]. Besides, the LC3-II (as ortholog of Atg8) and Atg12-Atg5-Atg16L conjugation systems are also essential for the autophagosomal formation [29] [35]. In addition to Atg proteins, many other factors and proteins, including Ras-related protein Rab-7/5A (Rab7/5A), Lysosomal-associated membrane protein 1/2 (Lamp1/ Lamp2), ATPase, Vacuolin-1, TPCs and TRPMLs have been implicated in regulating autophagosomal lysosomal fusion process [35] [38] [39] [40].

In the end, the completion of autophagy depends on lysosomal activity, deficiencies in autophagosomal lysosomal fusion and degradation can lead to the accumulation of autophagosomes, ultimately impairing cells or resulting in cell death [41]. Accordingly, the mechanisms of the control for lysosome function are emerging as an important theme for autophagy-lysosomal cargos digestion.

3. CD38 and Autophagy

Because lysosomes play an important role in autophagy, the regulation mechanism of lysosomal functions is considered as the key element for autophagy. The fact that autophagy involves degradation by the autolysosome, which is formed by conjugation of an autophagasome and a lysosome, suggests that CD38/NAADP signaling might be implicated in this process (Figure 3). It is known that CD38-mediated regulation of lysosome function contributes to autophagic flux or autophagy maturation. However, as listed in Table 1, there is paradox about the effect of CD38 on autophagy. The summary of these evidences are described as below.

3.1. The Positive Regulation of CD38 in Autophagy

Most lines of evidence support the positive regulation of CD38 in autophagy. Cumulating evidence has suggested that lysosome trafficking and fusion to autophagosomes is positively modulated by NAADP via CD38 enzymatic activity [19] [42]. Deficiency of CD38 resulted in a defective autophagic event in coronary arterial media of mice [22] [43]. Inhibition of CD38 by CD38 shRNA or nicotinamide leads to accumulation of p62 and autophagosomes, suppressing lysosome fusion to autophagosomes [44]. Moreover, in indolocarbazole induced
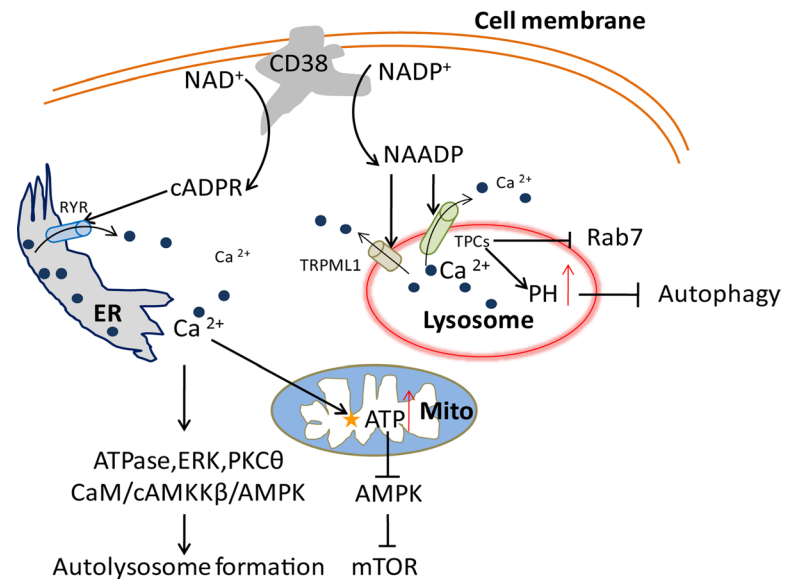
Figure 3. The potential mechanisms of CD38 in autophagy regulation. CD38 acts as a NAD$^+$ dependent enzyme, which catalyzes the synthesis of cADPR and NAADP from NAD$^+$ and NADP$^+$, respectively. Then, the cytosolic cADPR and NAADP target to RYR on ER and TPC or TRP-ML1 on lysosome, modulating ER-Ca^{2+} signaling and lysosome-Ca^{2+} signaling, respectively. On the one hand, increasing of intracellular Ca^{2+} leads to activation of dynein ATPase, ERK, PKCθ or cAMKKβ/AMPK signaling pathways, thus facilitates the formation of autolysosome. On the other hand, Ca^{2+} releases promote ATP synthesis in mitochondria (Mito) and AMPK inhibition, lead to suppression of mTOR and autophagy. Moreover, releasing of Ca^{2+} from lysosome by TPC2 or TRPML-1 has been suggested to inhibit Rab7 and alkalinizing lysosomal pH, thereby results in suppression of autophagosomal-lysosomal fusion, accumulation of autophagosomes in cytosol and subsequently autophagy impairment.

cell autophagy, CD38 expression and the LC3-II/LC3-I ratio are significantly elevated in response to ZW2-1 [45]. Subsequent studies showed that enzymatic activity of CD38 to produce NAADP plays an essential role in the following breakdown of the autophagic contents [19]. When nucleosidase activity of CD38 is disrupted or NAADP production is decreased, the formation of autolysosomes and degradation of autophagic vesicles also become impaired, which promotes cell dedifferentiation, proliferation and growth [19]. Besides, NAADP is also reported to increase acidic vesicular organelle formation and the expression levels of LC3II and Beclin-1 [46]. It is known that ROS promote autophagy maturation by regulating dynein-mediated autophagosomes trafficking [47]. High glucose induced ROS production results in the activation of dynein ATPase, which further triggers autophagosomes trafficking and fusion with lysosomes [47]. Moreover, antagonism of NAADP mediated Ca^{2+} signaling with NED-19 and pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid (PPADS) eliminated ROS-evoked lysosomes Ca^{2+} flux and dynein activation [47].

3.2. The Negative Regulation of CD38 in Autophagy

In contrast, CD38 is also involved in inhibition of autophagy. Some lines of evi-

Table 1. The roles of CD38 in autophagy. Abbreviation: Embryonic stem cells, ESC; Chronic lymphocytic leukemia, CLL; Immature hematopoietic progenitors, IHP; Coronary arterial myocytes, CAM; Mouse glomerular podocytes, MGP; Vascular endothelial cells, VEC; Vascular smooth muscle cells, VSMC.

Cell types	Potential Mechanism	Effect to autophagy	References (first author, year)
CAM	NAADP-Lysosome-Ca^{2+}	Positive	Zhang, 2010
CAM	Autophagic flux	Positive	Xu, 2011
Astrocytes	NAADP/TPCs, LC3-II, Beclin-1	Positive	Pereria, 2011
VEC, VSMC	NAADP/TRPML1/TPCs	Positive	Li, 2013
MGP	LC3-II	Positive	Xiong, 2013
CAM	Autophagic flux	Positive	Zhang, 2014
CAM	Dynein ATPase	Positive	Xu, 2014
B cells	Blimp1, Beclin-1/p62	Positive	Yuan, 2014
293T cells	NAADP/TRPML1, LRRK2/CaMKK/AMPK	Negative	Gomez-Suaga, 2012
CLL cells	Beclin-1, Bcl-2, Autophagic flux	Negative	Bologna, 2013
Hela cells, ESC	NAADP/TPC2/Ca^{2+} signaling, lysosomal pH	Negative	Lu, 2013
ESC	NAADP/TPC2/Ca^{2+} Signaling	Negative	Lu, 2013
IHP	Autophagic flux	Negative	Gomez-Puerto, 2016

dence indicate that CD38 is a autophagy suppressor. Deficiency of CD150 is associated with increased expression levels of CD38 and inhibited phosphorylation of p38, JNK1/2, Bcl-2 and autophagic flux [7]. Moreover, CD38 deficiency immature hematopoietic progenitors show a higher autophagic flux as shown by analysis of LC3-II and p62 levels, as well as flow cytometry-based autophagic vesicle quantification [48]. NAADP as a potent Ca^{2+} mobilizing messenger, which targets the TRPMLs or TPCs and triggers Ca^{2+} release from the endolysosomal stores [19]. As we known, the members of the TRPML constitute a family of evolutionarily conserved cation channels that play crucial roles in endolysosomal vesicles [20] [49]. TRPMLs localize to endolysosomes and facilitate Ca^{2+}-dependent fusion between autophagosomes and lysosomes resulting in lysosomal degradation of autophagic material [20]. It is known that TPCs have recently emerging as the targets for NAADP, which are crucial for appropriate basal and induced autophagic flux in cardiomyocytes [50]. For instance, overexpression of TPC2 *in vitro* suppressed autophagosomal-lysosomal fusion, thereby resulting in the decreasing levels of LC3-II and p62 and the accumulation of autophagosomes, suggesting that inhibition of autophagy progression by TPC2 [39] [41]. Thus, NAADP and its receptors (TRPMLs or TPCs) in lysosome may play crucial roles in lysosomal functions and subsequent autophagy events.

3.3. The Potential Mechansim of CD38 in Autophagy

It is well established that intracellular Ca^{2+} is one important regulators of autophagy [21]. Firstly, intracellular Ca^{2+}-mobilization stimulates calmodulin (CaM),

ERK and PKCθ signaling, thereby mediating autophagy progression. Of note, overexpression of leucine-rich repeat kinase 2 (LRRK2) stimulates an increase in autophagy initiation through Ca^{2+}-dependent activation of a CaMKKβ/adenosine monophosphate (AMP)-activated protein kinase (AMPK) pathway [51] [52]. Moreover, Ca^{2+} also inhibits autophagy by promoting mitochondria ATP, which inhibits CaMKKβ/AMPK pathway [21]. Thus, CD38 triggers intracellular Ca^{2+} flux from ER and lysosome can also result in opposite outcomes of autophagy directly, depending on multiple stimuli and the different cellular state. As illustrated in Figure 3, CD38 catalyzes the synthesis of cADPR and NAADP from NAD and NADP, respectively. These two messengers target to RYR and TPC or TRP-ML1, modulating ER-Ca^{2+} signaling and lysosome-Ca^{2+} signaling, respectively. On the one hand, increasing of intracellular Ca^{2+} leading to activation of dynein ATPase, ERK, PKCθ or cAMKKβ/AMPK signaling pathways, thus facilitates the formation of autolysosome. On the other hand, Ca^{2+} releases promoting ATP synthesis in mitochondria and AMPK inhibition, leading to suppression of mTOR and autophagy. In addition, releasing of Ca^{2+} from lysosome by TPC2 or TRPML-1 have been suggested to inhibit Rab7 and alkalinizing lysosomal pH, thereby resulting suppression of autophagosomal-lysosomal fusion, accumulation of autophagosomes in cytosol and subsequently autophagy impairment.

Indeed, CD38 is involved in various stimuli induced autophagy. FasL has been shown to significantly increase NAADP production and intracellular Ca^{2+} flux in CD38 overexpressed mice [53]. In experimental autoimmune myocarditis mouse model, IL-17 promote B cell autophagy by controlling B-lymphocyte- induced maturation protein-1 (Blimp-1) expression and CD38$^{(+)}$ CD138$^{(+)}$ B cell percentages [54]. Not surprisingly, CD38 is possibly implicated in autophagy by variety of mechanisms. Lu *et al.* demonstrated that Vacuolin-1 suppress general endosomal-lysosomal degradation by decreasing V-ATPase activity to enhance lysosomal pH in HeLa cells [38]. Of interest, in addition to CD38, other NAD$^+$ dependent enzymes, such as silent information regulator 2-related enzymes (Sirtuins) and the polymerase (ADP-ribose) polymerases (PARPs), act as the key mediators of macro autophagocytotic cell death [55] [56]. There is a potential crosstalk among CD38, Sirtuins and PARPs in autophagic cell death and survival pathways [56].

Taken together, there are several potential mechanisms of CD38 in autophagy, including 1) mobilizing intracellular Ca^{2+} release by producing cADPR and NAADP, 2) affecting the functions of lysosome by regulating the activity of lysosome related proteins, e.g. TPC2, Vacuolin-1, and 3) crosstalking with other NAD$^+$-dependent enzymes, e.g. Sirtuins, PARPs. Thus, continuing to study the mechanism of CD38 and its related proteins in autophagy is very interesting works.

4. Conclusion

In conclusion, CD38 acts as an important autophagy modulator by predomi-

nantly regulating CD38/NAADP/Ca^{2+} signaling mechanism. CD38 may be playing a dual effect on autophagy process in response to multiple different stimuli. A complete understanding the molecular mechanism of CD38 in autophagy remains in a fascinating challenge for future investigation.

Acknowledgements

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