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Beclin 1
A role in membrane dynamics and beyond

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Abbreviations: Ambra1, activating molecule in Beclin 1-regulated autophagy; ARF, alternative reading frame; Atg, autophagy-related; Barkor, Beclin 1-associated autophagy-related key regulator; Bcl-2, B-cell lymphoma-2; Bcl-x_L, B-cell lymphoma extra long; Beclin 1, Bcl-2-interacting myosin-like coiled-coil protein; BH3, Bcl-2 homology domain 3; Bif-1, endophilin B1; CCD, coiled-coil domain; CD4, cluster of differentiation 4; CDDP, cis-diamminedichloroplatinum; DAPK, death-associated protein kinase; ECD, evolutionarily conserved domain; EGFR, epidermal growth factor receptor; EEA1, early endosome antigen 1; ER, endoplasmic reticulum; FoxO3, Forkhead box 3; γHV68 M11, gamma herpesvirus-68 M11; GAS, Group A *Streptococcus*; HIF-1α, Hypoxia-inducible factor 1α; HIV, human immunodeficiency virus; HMGB1, high mobility group box 1; HSV, herpes simplex virus; IFN, interferon; JNK, c-jun N-terminal kinase; KSHV v-Bcl-2, Kaposi's sarcoma-associated herpes virus-derived Bcl-2 homolog; LC3, microtubule-associated protein 1 light chain 3; M2, influenza A virus matrix protein 2; NFκB, nuclear factor κB; PAS, phagophore assembly site; PtdIns3KC3, phosphatidylinositol 3-kinase class III; PtdIns(3)P, phosphatidylinositol 3-phosphate; RME-8, receptor-mediated endocytosis-8; Rubicon, RUN domain and cysteine-rich domain containing Beclin 1-interacting protein; TLR, Toll-like receptor; TRAF6, TNF receptor associated factor 6; UVRAG, UV-radiation resistance associated gene; Vps, vacuolar protein sorting

Beclin 1 (Atg6) is a well-known key regulator of autophagy. Although Beclin 1 is enzymatically inert, it governs the autophagic process by regulating PtdIns3KC3-dependent generation of phosphatidylinositol 3-phosphate (PtdIns(3)P) and the subsequent recruitment of additional Atg proteins that orchestrate autophagosome formation. Furthermore, Beclin 1 is implicated in numerous biological processes, including adaptation to stress, development, endocytosis, cytokinesis, immunity, tumorigenesis, aging and cell death. Whether all of these processes involve only the autophagy-inducing function of Beclin 1 is now being seriously questioned, because Beclin 1 appears to exercise several non-autophagy functions. Therefore, we should broaden our view of Beclin 1 as a specialized molecule in autophagy to that of a multifunctional protein. The central role of Beclin 1 in multiple signaling events obviously requires tight regulation at multiple levels. Its function is kept in check by diverse mechanisms, such as epigenetic silencing, microRNA regulation, post-translational modifications, and protein-protein interactions. Interestingly, multiple diseases are associated with deficiency or malfunction of Beclin 1, which makes it a potentially valuable target for various therapies, including anticancer treatment. In this review, we focus on Beclin 1 as a multifunctional protein, discuss the variety of mechanisms by which it is controlled, and give an overview of Beclin 1-associated pathologies.

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Introduction

In the late 1990s, Beclin 1, a coiled-coil protein, was discovered as a direct interactor of the anti-apoptotic B-cell lymphoma-2 (Bcl-2) protein and was therefore given the name Bcl-2-interacting myosin-like coiled-coil protein (Beclin 1).[1] Beclin 1, also named Atg6, is highly conserved in eukaryotes and belongs to the autophagy-related (Atg) family of proteins, which are key regulators in autophagy.[2] To date, more than 30 Atg proteins have been identified in yeast and about half of them have mammalian orthologs. Distinct types of autophagy have been described, including macroautophagy, microautophagy, and chaperone-mediated autophagy. Macroautophagy, hereafter referred to as autophagy, is the best characterized. It is a catabolic process involved in recycling of amino acids, nucleotides and lipids: superfluous proteins and organelles are sequestered in double-membrane vesicles (autophagosomes) and degraded in lysosomes.[3] In this way, autophagy also leads to the removal of misfolded proteins, protein aggregates and damaged organelles, such as mitochondria and endoplasmic reticulum, which could harm the cell.[4] Importantly, increased autophagy is a primary response to cellular stress in an attempt to survive unfavorable conditions, such as nutrient or growth factor depletion, heat or hypoxia. Thus, autophagy is a major cytoprotective mechanism. Conversely, cell death can be accompanied by the presence of autophagic vacuoles, and this finding gave rise to the term "autophagic cell death."[5] Clearly, autophagy is interconnected with cell death pathways, such as those of apoptosis and necrosis, but how these signaling pathways interrelate (independently, cooperatively or in opposition) appears to depend on the cell type and the stimulus.[6-8]

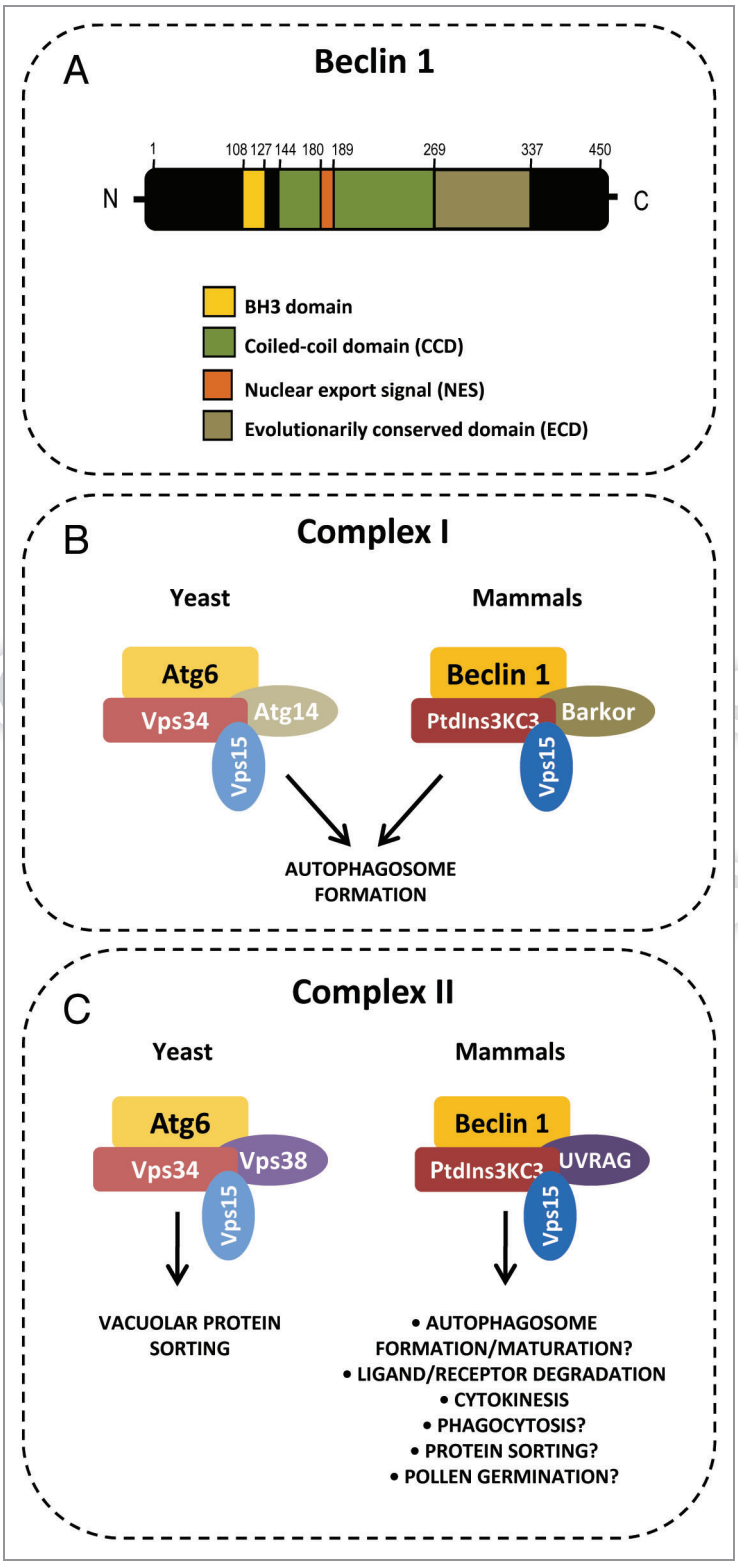

Figure 1. Schematic representation of the Beclin 1 protein and the PtdIns3KC3 complexes I and II in yeast and mammals. (A) Schematic representation of the Beclin 1 protein and its domains. (B) Complex I, composed of Beclin 1 (Atg6), PtdIns3KC3 (Vps34), p150 (Vps15) and Atg14 (Barkor) is implicated in autophagosome formation both in mammals and yeast. Functions of complex II, containing Beclin 1 (Atg6), PtdIns3KC3 (Vps34), p150 (Vps15) and UVRAG (Vps38) are still largely unclear or debated. Complex II functions in autophagosome formation, ligand/receptor degradation and cytokinesis, and potentially is implicated in phagocytosis and protein sorting. In yeast, complex II is required for vacuolar protein sorting.

Autophagy is controlled by the phosphatidylinositol 3-kinase class III (PtdIns3KC3) complex, an autophagy-inducing complex that regulates autophagosome formation. One of its key components is Beclin 1, which acts as the platform for its assembly and stimulates its activity.[9] When PtdIns3KC3 is activated, phosphatidylinositol 3-phosphate [PtdIns(3)P] is generated, enabling the recruitment of other Atg proteins involved in autophagosome biogenesis.[10,11] Although the Beclin 1-PtdIns3KC3 axis is in charge of most autophagy responses, certain triggers (e.g., resveratrol, methyl-4-phenylpyridinium, GX15-070/obatoclax) induce an autophagy pathway that is independent of Beclin 1.[12-15] However, Beclin 1 is not only a key player in autophagy but also serves non-autophagy functions, such as in endocytic trafficking, phagocytosis, control of cytokinesis, and pollen germination. In this review we give an overview of the current state of knowledge about Beclin 1, with special attention to the diversity of its functions and regulation.

Beclin 1 Complexes

Shortly after its discovery as a Bcl-2 interactor, Beclin 1 was shown to play a central role in autophagy. Beclin 1 can restore starvation-induced autophagy in *ATG6*-disrupted yeast strains and human breast carcinoma cells lacking detectable Beclin 1 levels, whereas Beclin 1 overexpression activates autophagy.[16] In line with these observations, autophagy is defective in Beclin 1-deficient embryonic stem cells.[17] Remarkably, *Beclin 1* knockout mice die early during embryogenesis, and this clearly demonstrates its importance during development.[17,18]

Beclin 1 is a 60-kDa protein containing a Bcl-2 homology domain (BH3), a coiled-coil domain (CCD) and an evolutionarily conserved domain (ECD); these domains enable multiple protein interactions (**Fig. 1A**).[19-23] Through its ECD, Beclin 1 binds PtdIns3KC3, which is required for PtdIns3KC3-dependent generation of PtdIns(3)P and the subsequent recruitment of additional Atg proteins that orchestrate autophagosome formation.[10] Interestingly, Beclin 1 forms large homo-oligomers due to interaction of the CCD and BH3 domains.[24,25] Beclin 1 multimerization is needed for the recruitment and consequent concerted action of other autophagy-inducing factors.[20,24] Two stable Atg6/Beclin 1 complexes have been described in both yeast and mammals. Atg6/Beclin 1, Vps34/PtdIns3KC3 and Vps15/p150 (regulatory protein kinase of Vps34/PtdIns3KC3) constitute the central platform that binds different proteins during different stages of autophagic signaling (**Fig. 1B and C**). On the one hand, this

platform binds Atg14 or its mammalian homolog Atg14L (also called Beclin 1-associated autophagy-related key regulator, Barkor). This so-called complex I initiates autophagosome formation. To this end, Atg14/Atg14L directs complex I to the phagophore assembly site (PAS) or endoplasmic reticulum from which autophagosomes emerge.[26] On the other hand, complex II is generated by recruitment of Vps38 or its homolog UVRAG (UV-radiation resistance associated gene). In yeast, complex II is involved in vacuolar protein sorting, suggesting a similar function of this complex in mammals. Originally, in mammals, complex II had been implicated in autophagosome formation.[27] However, this theorem has been debated and recent studies rather indicate the existence of autophagy-independent roles of complex II.[28-31] Current research has implicated complex II in ligand/receptor degradation and cytokinesis.[29] Also, data in murine macrophages and *C. elegans* demonstrate a role for Beclin 1 in endocytosis and protein sorting (see below).[29-31] However, whether this function depends on the interaction with UVRAG (or a potential ortholog) needs further investigation. It is of note that UVRAG can also function independently of Beclin 1 (and hence complex II), for instance in autophagosome and endosome maturation.[27,28,32]

Interestingly, additional Beclin 1 interacting proteins, including Ambra1, Bif-1 (endophilin B1), Rubicon (RUN domain and cysteine-rich domain containing Beclin 1-interacting protein) and Bcl-2 have been identified that stimulate or inhibit either of the two stable complexes (**Table 1**) (extensively reviewed in ref. 65). These interactions are mainly transient and rather occur under specific conditions, which is of major interest for studying the mechanisms that regulate complex I and II activities under diverse patho(physiological) conditions.

Beclin 1 and the Regulation of its Platform Function in Autophagy

Sufficient levels of Beclin 1 are necessary for its autophagic function. Indeed, human breast MCF7 carcinoma cells in which Beclin 1 is undetectable, and *Beclin 1*$^{+/-}$ mice have impaired autophagy.[16,66] However, little is known about *Beclin 1*'s transcriptional regulation. Some reports demonstrate increased Beclin 1 expression under certain conditions, for example during starvation of chondrocytes, in atrophying muscle cells, and during ischemia/reperfusion of the heart.[67-69] In line with these observations, several transcription factors, for example, FoxO3, NFκB, HIF1α, c-Jun and E2F1, drive Beclin 1 expression, and detailed studies of the *BECN1* promoter unveiled the presence of binding sites for E2F1, c-Jun and NFκB (**Fig. 2A**).[67,69-74] Interestingly, miRNA30a binding sequences were found in the 3' UTR of *BECN1* (**Fig. 2B**).[75] MicroRNAs regulate protein expression by hampering protein synthesis or triggering mRNA degradation. Treatment of tumor cells with a miRNA30a mimetic decreases *BECN1* mRNA and the corresponding protein levels. Additionally, a dense cluster of CpG islands is found between the 5' end and intron 2 of the *BECN1* gene.[76] Hypermethylation of this cluster in some sporadic breast tumors results in decreased expression of Beclin 1 (**Fig. 2A**).[76] Beclin 1 protein levels are also controlled by calpain-mediated degradation and caspase-dependent cleavage (**Fig. 2C**).[77-82] The Beclin 1 fragments generated by caspases are unable to induce autophagy, demonstrating that a proteolysis-dependent mechanism controls Beclin 1 function.[79,80]

Beclin 1 is also kept in check at the post-translational level. Protein-protein interactions, for example, are very important for regulating Beclin 1's function in autophagy. Bcl-2 and Bcl-x_L directly bind the BH3 domain of Beclin 1 and effectively counteract Beclin 1-dependent autophagy (**Fig. 3A**).[20,23] This finding demonstrates that, in addition to their well-characterized anti-apoptotic role, Bcl-2 and Bcl-x_L are able to suppress autophagy. Furthermore, this finding was the first clue of the existence of a crosstalk between the apoptotic and the autophagic pathways. Although the Beclin-1–Bcl-2 interaction inhibits the pro-autophagic function of the former, it seems not to affect the anti-apoptotic role of Bcl-2.[83] The importance of the Bcl-2/Bcl-x_L-Beclin 1 interaction in autophagy is emphasized by the fact that formation or persistence of this complex is influenced by several autophagy-regulatory mechanisms, such as post-translational modifications (**Fig. 3A**). Phosphorylation and ubiquitination of Beclin 1 and Bcl-2 can either stabilize or dissociate the Beclin-1–Bcl-2 complex, which leads to inhibition or initiation of autophagy, respectively. When DAPK (Death-Associated Protein Kinase), a serine/threonine kinase important in apoptosis regulation, phosphorylates Thr119 in the BH3 domain of Beclin 1, Beclin 1-Bcl-x_L dissociates and formation of autophagosomes increases.[52] Similarly, binding of Bcl-2 to Beclin 1 is abrogated when JNK1 (Jun N-terminal kinase 1) phosphorylates Bcl-2 (Thr69, Ser70, Ser87).[37] Interestingly, JNK1 preferentially targets ER-localized Bcl-2, which, in contrast to mitochondrial Bcl-2, affects Beclin 1's function in autophagy.[20,37] Whether Bcl-2 can also influence other functions of Beclin 1 is not known. However, this could be of huge interest since Beclin 1 has now been implicated in non-autophagy processes (see below). Beclin 1 and Bcl-2 are both also targeted for ubiquitination. TNF receptor associated factor 6 (TRAF6)-dependent ubiquitination of Beclin 1 occurs in response to Toll-like receptor (TLR) signaling and to treatment of macrophages with interferon-γ (IFNγ) or interleukin-1 (IL-1).[51] In addition, K63-linked ubiquitination of Beclin 1 at Lys117 promotes Beclin 1 oligomerization and consequent induction of autophagy, probably by stimulating PtdIns3KC3 activity.[51] In line with this observation, TLR4-induced autophagy is counteracted when TRAF6 and Beclin 1 are deubiquitinated by A20.[51] Similar to the effect of phosphorylation of Bcl-2, ubiquitination of Bcl-2 was suggested to influence the Bcl-2-Beclin 1 interaction and consequent initiation of autophagy. Bcl-2 was identified as a new substrate for Parkin, an E3-ligase that is mutated in familial and sporadic Parkinson disease.[84] Parkin-dependent mono-ubiquitination of Bcl-2 stabilizes the Bcl-2 protein and enhances its binding to Beclin 1, thereby inhibiting both basal and starvation-induced autophagy. However, it has also been suggested that Parkin is involved in the positive regulation of mitophagy. To this end, Parkin is recruited to damaged mitochondria in a PINK1-dependent manner and poly-ubiquitinates VDAC1 (Voltage-dependent anion channel 1) among other proteins.[85,86]

Table 1. Beclin 1 interacting proteins and their autophagy-related functions

ID	Interactor	Function	Ref.
BH3	Bcl-2	Inhibition of Beclin 1-dependent autophagy Suppresses Beclin 1-PtdIns3KC3 interaction Suppresses Beclin 1-UVRAG binding Increases Beclin 1-Ins(1,4,5)P_3R binding	20, 33, 34
	Bcl-x_L	Inhibition of vesicle nucleation	1, 23, 35, 36
	Mcl-1	Inhibition of vesicle nucleation	23
	KSHV v-Bcl-2	Inhibition of Beclin 1-dependent autophagy	20, 37
	γHV68 M11	Inhibition of Beclin 1-dependent autophagy	38, 39
CCD	Atg14/Barkor	Vesicle nucleation Vesicle expansion Autophagosomal targeting of Beclin 1	27, 40, 41
	Bif-1*	Vesicle nucleation (membrane bending) PtdIns3KC3 activation Tumor suppression	42
	nPIST	Induction of autophagy after GluRδ2^{Lc} activation	43
	Rubicon*	Inhibition of vesicle maturation	28, 40
	UVRAG/Vps38	Vesicle nucleation? Vesicle maturation Tumor suppression	27, 29, 44, 45
	Beclin1/Atg6	Vesicle nucleation PtdIns3KC3 activation Tumor suppression	17, 18, 24, 25, 29, 46, 33
ECD	PtdIns3KC3/Vps34	Vesicle nucleation Lipid kinase: generation of phosphatidylinositol 3-phosphate (PtdIns(3)P) Tumor suppression	10, 29, 32
	NLRP4	Inhibition of autophagy	47
aa 141–150	Ambra1	Vesicle nucleation PtdIns3KC3 activation Neurodevelopment Cell proliferation Mediates Beclin 1-cytoskeleton interaction Competes with Bcl-2 for binding Beclin 1	48, 49, 50
aa 54–58 and aa 297–301	TRAF6	Induction of autophagy after TLR4 triggering K63-linked ubiquitination of Beclin 1	51
Unknown	DAPK	Induction of autophagy Phosphorylation of Beclin 1 Disruption of Beclin 1-Bcl-2 interaction	52
	HMGB1	Induction of autophagy in response to ROS Competition with Bcl-2 for Beclin 1 binding	53
	Ins(1,4,5)P_3R	Inhibition of autophagy through Bcl-2-Beclin 1 binding	34
	MYD88	Induction of autophagy after TLR (4 and 7) triggering Competition with Bcl-2 for Beclin 1 binding	54, 55
	Pink1	Induction of mitophagy	56
	Rab5	Vesicle nucleation PtdIns3KC3 activation Positive regulation of Atg12–Atg5 conjugation	57
	Survivin	Induction of autophagy	58
	TRIF	Induction of autophagy after TLR (3 and 4) triggering Competition with Bcl-2 for Beclin 1 binding	54
	A20	Inhibition of autophagy Deubiquitination of Beclin 1 Inhibition of TRAF6-mediated ubiquitination of Beclin 1	51
	VMP1	Vesicle nucleation Recruitment of Beclin 1 to autophagic membrane	59
	Nef	Inhibition of autophagosome maturation	60
	SLAM	Triggers phagosome maturation	61
	ICP34.5	Inhibition of autophagosome formation Represses activation of $CD4^+$ T cells	62, 63
	M2	Inhibition of autophagosome maturation	64

Interactors marked with an asterisk (*) were shown to interact with Beclin 1 through UVRAG. ID, interacting domain; BH3, Bcl-2 homology domain; CCD, coiled-coil domain; ECD, evolutionarily conserved domain

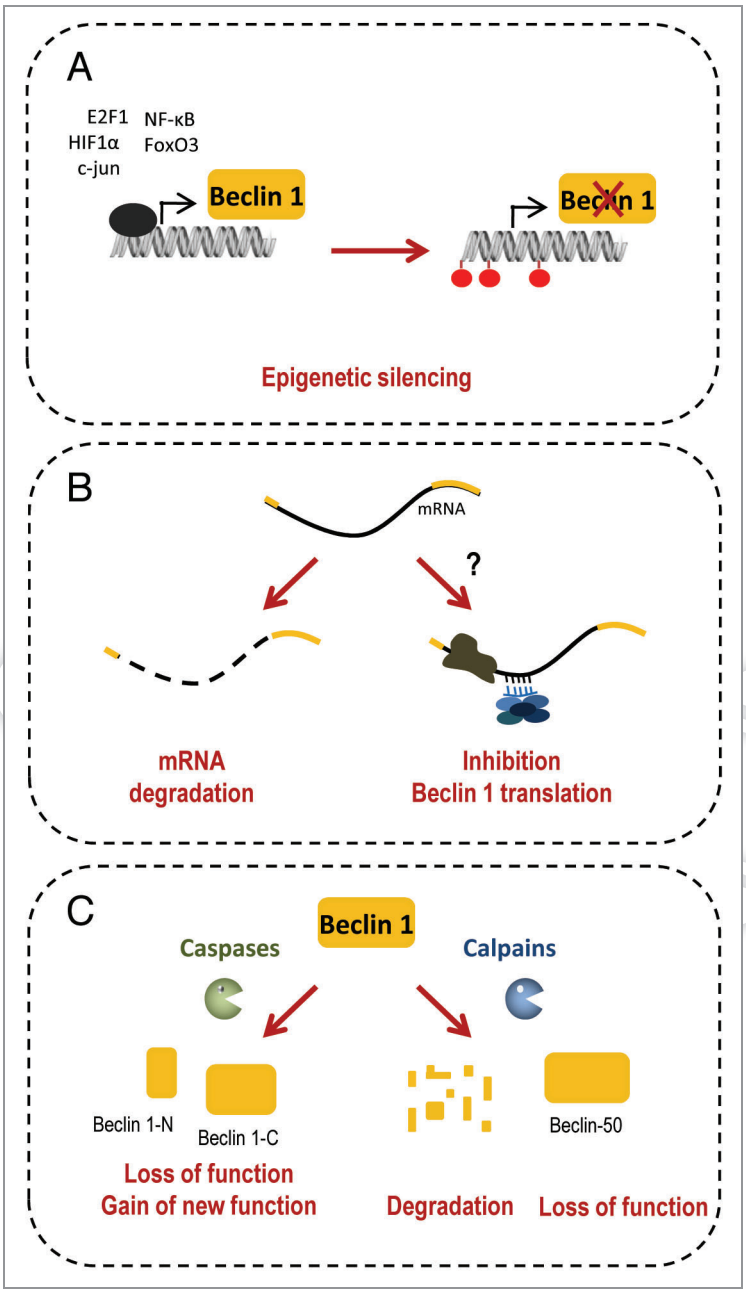

Figure 2. Schematic overview of the mechanisms regulating Beclin 1 expression. (A) Transcriptional regulation of *BECN1*. Several transcription factors (EF1, c-jun, NFκB, FoxO3, HIF1α) increase Beclin 1 expression. Conversely, hypermethylation of CpG islands in the *BECN1* gene causes epigenetic silencing and reduced Beclin 1 expression levels. (B) miRNA regulation of *BECN1* mRNA and protein levels through mRNA degradation and inhibition of protein translation. (C) Regulation of Beclin 1 protein levels through proteolytic cleavage or degradation. During apoptosis, caspases cleave Beclin 1 at specific sites, abrogating its autophagic function, but also resulting in two defined Beclin 1-derived fragments fulfilling new functions. Calpain-mediated cleavage of Beclin 1 results in the formation of a 50-kDa fragment (Beclin-50) or complete degradation of the protein.

The Bcl-2-Beclin 1 complex can also be disrupted by competitive binding of pro-apoptotic proteins, such as tBid, Bad and BNIP3, which have higher affinity than Beclin 1 for the BH3 domain of Bcl-2.[21,87] Likewise, ARF (alternative reading frame) binds Bcl-x_L and abrogates Bcl-x_L-Beclin 1 binding.[88] In addition, HMGB1 was recently shown to bind Beclin 1 and to dissociate the Bcl-2-Beclin 1 complex.[53]

Finally, recent data demonstrate regulation of Beclin 1-dependent autophagy at the level of subcellular localization (**Fig. 3B**). Under normal conditions, binding of Beclin 1 to the cytoskeleton prevents it from promoting autophagy at the ER.[26,48] This microtubule-associated localization is mediated by Ambra1 via its interaction with the dynein complex. Upon induction of autophagy, ULK1 phosphorylates Ambra1 and allows the release of the PtdIns3KC3 complex, which translocates to the ER to activate autophagy.[48] In this way, Beclin 1 is held in check by sequestration of the Beclin 1 interactome at the cytoskeleton. Interestingly, Bcl-2 directly binds a pool of Ambra1 at the mitochondria, which prevents Ambra1 from associating with Beclin 1. Autophagy induction results in dissociation of Bcl-2–Ambra1, allowing Beclin 1 to bind Ambra1 and autophagosomes to form.[49]

Beclin 1 Functions Beyond Autophagy

For more than a decade it has been clear that Atg6 also exerts non-autophagy functions in yeast. Atg6 is part of the protein sorting machinery.[89] Vacuolar protein sorting (Vps) is a part of the secretory and endocytic pathways, which is responsible for sorting and targeting of vacuolar hydrolases (e.g., carboxypeptidase Y) from the late-Golgi network to the yeast vacuole, where they can be processed into their mature forms.[10,90] In part, Atg6 is required for proper recycling of the sorting receptor Vps10 and other late-Golgi proteins from the pre-vacuolar endosome to the Golgi.[89] To this end, Atg6, Vps34 and Vps15 bind Vps38 within complex II and direct the synthesis of PtdIns(3)P on endosomal membranes, which is required for retromer recruitment (**Fig. 1C**). Interestingly, UVRAG, which was identified as the mammalian ortholog of Vps38, also forms an analogous complex II with Beclin 1, PtdIns3KC3 and p150.[44] Although this finding suggested a similar function for Beclin 1 in protein sorting in mammals, human Beclin 1 cannot restore Vps defects in *Atg6* disrupted yeast.[16] The relatively low amino acid sequence identity (24%) shared by human and yeast Atg6 might account for this functional difference between the two proteins. Whereas yeast Atg6 consists of 557 amino acids, mammalian Beclin 1 contains only 450, which may explain a more restricted functionality of the latter. Nevertheless, similar to yeast, the identification of two stable Beclin 1 complexes involving mammalian orthologs of Atg14 and Vps38 suggests a multifunctional role of Beclin 1 in cellular processes.[26,27,32] Furthermore, *Beclin 1* knockout in mice is embryonically lethal, which is in contrast to most other *Atg* genes (*Atg3*, *Atg4C*, *Atg5*, *Atg7*, *Atg9*, *Atg16L1* and *ULK1*).[17,18] This phenotypic difference can be explained by a lack of redundant mechanisms,

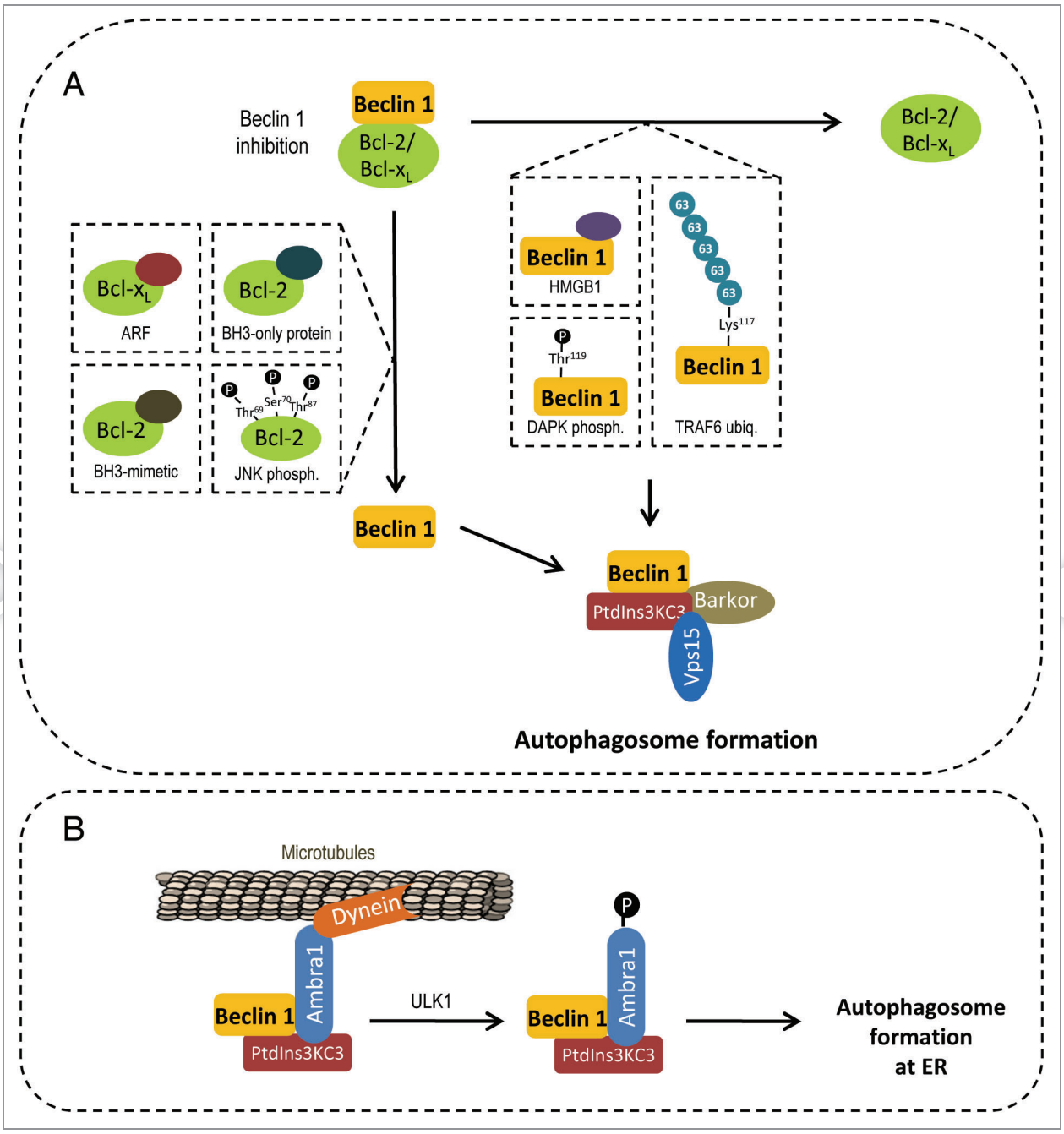

Figure 3. Schematic overview of the mechanisms regulating Beclin 1 activity. (A) Post-translational modification events triggering the dissociation of the Bcl-2/Bcl-x_L-Beclin 1 complex, resulting in Beclin 1 activity. Bcl-2 (Bcl-x_L) can be dissociated from Beclin 1 through competitive binding of BH3-only proteins or BH3-mimetics (or ARF), or JNK-mediated phosphorylation of Bcl-2 at Thr69, Ser70 and Thr87. In addition, Beclin 1 can be released from its inhibitors through HMGB1-binding, DAPK-mediated phosphorylation at Lys119 or TRAF6-dependent K63-linked ubiquitination of Beclin 1 at Lys117. Beclin 1 liberated from the Bcl-2/Bcl-xL-Beclin 1 interaction promotes autophagy. (B) Regulation of Beclin 1-dependent autophagy at the level of subcellular localization. Ambra1-mediated binding to the microtubules targets the PtdIns3KC3-complex to the cytoskeleton in non-autophagy conditions. Upon autophagy activation, Ambra1 is phosphorylated, which releases Ambra1 and the PtdIns3KC3-complex from the cytoskeleton and enables translocation of the PtdIns3KC3-complex to the ER for autophagosome formation.

which could compensate for the loss of Beclin 1 activity, as is the case for ULK1 and Atg4C.[91,92] However, it could also indicate distinct functions of Beclin 1 beyond autophagy. Indeed, accumulating evidence supports a role for Beclin 1 in non-autophagy processes.

For example, Beclin 1 functions in endocytosis. In complex with p150, PtdIns3KC3, UVRAG and Bif-1, Beclin 1 is involved in the downregulation of the epidermal growth factor receptor (EGFR) in HeLa cells.[29] Interestingly, although Atg14L knockdown results in impaired autophagy, it does not affect EGFR

internalization and degradation, indicating that Atg14L is dispensable in this process, and that Beclin 1 functions in an autophagy-independent way in this case. The role of Beclin 1 in the endocytic pathway has also been demonstrated in macrophages. Upon TLR signaling, Beclin 1 rapidly translocates to the phagosomes and mediates efficient phagosome-lysosome fusion to ensure rapid acidification and efficient destruction of the pathogen.[31] Even though the plasma membrane has been reported to contribute to autophagosome formation, translocation of Beclin 1 to phagosomes during phagocytosis does not seem to involve autophagosome formation, which again supports the hypothesis that Beclin 1 has non-autophagy functions during endocytosis.[31,93] Also, Beclin 1 is involved in apoptotic cell clearance during cavitation.[94,95] Beclin-1-deficient embryoid bodies fail to generate crucial engulfment signals (phosphatidylserine and lysophosphatydylcholine), an energy-dependent process that is suggested to require autophagic signaling.[95] However, it still has to be clarified whether impairment of the function of the engulfing cells contributes to defective clearance of dead cells in Beclin 1-deficient embryoid bodies, which also might involve Beclin 1's function in phagocytosis. In *C. elegans,* ATG-6, the ortholog of Beclin 1, functions in endosome-to-Golgi retrograde transport.[30] Loss of *bec-1* activity results in aberrant sorting of MIG-14/Wntless, a retromer-dependent cargo protein. Instead of being transported to the Golgi, MIG-14/Wntless is misrouted to the lysosomal compartment in *bec-1* mutants and subsequently degraded. Similar observations were made using *vps34* mutants, suggesting that ATG-6 functions together with Vps34 in retrograde transport.[30] Further investigation is needed to determine the precise role of ATG-6 in retrograde transport. It is suggested that ATG-6 and VPS34 regulate endosomal recruitment of RME-8 (receptor-mediated endocytosis-8), a subunit of the retromer complex, through localized production of PtdIns(3)P.[30] Although it is tempting to speculate about the involvement of a similar complex II in this process, no ortholog of UVRAG has been identified in *C. elegans* so far. Collectively, these results implicate Beclin 1 or ATG-6 in protein trafficking (sorting of cell-surface receptors, retrograde transport and phagosome maturation). However, in contrast to this, an earlier publication reported results that argue against a role for Beclin 1 in endocytic trafficking.[96] In that study, *BECN1* knockdown did not affect EGFR degradation, trafficking of procathepsin D to the endosomal and lysosomal compartment or cell growth. The reason for these opposite findings is unclear. It is conceivable that Beclin 1's function in endocytosis could be cell type-specific or that residual, minute amounts of Beclin 1 due to incomplete knockdown still allow these processes to occur. Furthermore, the mechanism through which Beclin 1 contributes to endocytosis remains unsolved. In an analogy to yeast, one could hypothesize that Beclin 1 and Vps34 act cooperatively, perhaps through the localized generation of PtdIns(3)P on endosomes and phagosomes. PtdIns(3)P is crucial for proper endocytic membrane trafficking and phagosome maturation, and probably functions by recruiting effector proteins such as EEA1 (Early Endosomal Antigen 1) to the endosomal membrane. This idea is supported by data showing altered localization of PtdIns(3)P in *bec-1* mutant worms.[30]

Beclin 1 has also been implicated in cytokinesis control.[29,97] Knockdown of *Atg6* results in cytokinesis arrest and an increased number of multinucleated cells.[97] This cytokinesis is attenuated upon depletion of PtdIns3KC3, UVRAG and Bif-1, but not Atg14L, supporting the idea that also in this process Atg6 functions in an autophagy-independent manner.[29] As PtdIns3KC3, UVRAG and Bif-1 could be detected at the midbody, the PtdIns3KC3 complex is likely to exert its role in cytokinesis regulation specifically at this site.[29,97] In line with this, PtdIns(3)P and its effector FYVE-CENT (ZFYVE26), both of which are required for proper cytokinesis, localize at the midbody.

Finally, Beclin 1 also functions in non-autophagy pathways in plants as well. In *Arabidopsis thaliana*, *ATG6* disruption affects pollen germination and male fertility.[98,99] In support of an autophagy-independent function of ATG6 is the finding that none of the previously examined plant *ATG* mutants exhibit male gametophytic defects.[98,99] However, ATG6 deficiency apparently alters the expression of numerous genes, including some that are involved in autophagic signaling, suggesting the possible involvement of ATG proteins other than ATG6 in the process of pollen germination.

Together, these findings show that Beclin 1 participates in different signaling pathways and performs important functions in multiple cellular processes, such as autophagy, endocytosis, phagocytosis, cytokinesis and pollen germination. Although these processes look very different at first sight, each of them requires accurate membrane rearrangements and fluxes. Autophagy, endocytosis and phagocytosis depend on vesicle formation, trafficking and fusion, but cytokinesis and pollen germination also involve extensive vesicle transport for delivery of membrane and cell wall material during furrow (cytokinesis) and pollen tube formation (pollen germination).[100,101] The role of Beclin 1 in all of these processes can be probably brought back to a crucial function in membrane dynamics. Although it is not entirely clear what this particular function encompasses, it is very likely that it is a common mechanism that involves the controlled production of PtdIns(3)P via PtdIns3KC3 activation, which is a crucial event in each of these pathways for the recruitment of the appropriate effector proteins. Perhaps, as shown for Atg6 in yeast, the autophagic and non-autophagic functions of Beclin 1 are regulated by the binding of specific interactors that define its specific subcellular localization and determine its specific function in membrane trafficking. In addition, differential modification of Beclin 1 or its interactors could determine the pathway in which Beclin 1 engages. To clearly understand the pleiotropic function of Beclin 1, one should further explore the composition of the different Beclin 1 complexes in different settings, including the consecutive steps in autophagy, endocytosis, phagocytosis, cytokinesis and pollen germination.

Interestingly, recent reports reveal yet another role for Beclin 1. Although cell death is mainly linked to the autophagy-related function of Beclin 1, an increasing amount of data demonstrates autophagy-independent functions for Beclin 1 in cell death promotion.[15,80,102] During apoptosis, Beclin 1 is cleaved by caspases, resulting in cytotoxic fragments that initiate a positive feedback loop toward cell death.[79,80,102] While incapable of

Table 2. List of disorders linked with altered Beclin 1 expression levels and putative role of Beclin 1-mediated autophagy

Disorder	Beclin 1 modifications and putative role	Ref.
Huntington disease **Alzheimer disease** **Parkinson disease**	• Decreased Beclin 1 protein levels • Sequestration in aggresomes (Huntington) • Caspase-mediated cleavage (Alzheimer) • Role in removal of aggregate-prone mutant proteins (Huntingtin, β-amyloid, α-synuclein)	106, 107, 108–110
Sandhoff disease **Niemann-Pick C disease**	• Increased Beclin 1 levels • Protective role	111
Cystic fibrosis	• Beclin 1 crosslinking • Role in removal of misfolded and aggregate-prone mutant CFTR protein	112
Heart ischemia/reperfusion	• Ischemia: protective role • Reperfusion: increased Beclin 1 levels, destructive role of Beclin 1 (promotes myocardial injury)	68
Heart pressure overload	• Deterioration of contractile function	113
Cancer: breast, ovarian, prostate, brain, colon, liver	• Decreased Beclin 1 protein levels (age-related) • Mono-allelic deletions in *BECN1* • Loss of heterozygosity • Tumor-suppressor role, prevention of genome instability, inhibition of malignant transformation	16–18, 76, 78, 46, 114, 115, 116
Cancer: colorectal, gastric	• Increased Beclin 1 protein levels	117
Fatal encephalitis in mice	• Binding of HSV-1 ICP34.5 to host Beclin 1 • Role in restricting virus replication and neurovirulence	1, 62

inducing autophagy, one of the Beclin 1-derived fragments accumulates at the mitochondria and promotes the release of pro-apoptotic factors from mitochondria.[80,103] Notably, similar observations were made for Atg4D and Atg5 cleavage by caspases and calpains, respectively.[104,105] It is likely that more Atg proteins may have a similar fate. In this respect, a considerable part of the autophagy machinery might be targeted for specific proteolysis and subsequently converted into cytotoxic effector molecules that aid in the execution of cell death. These two faces of autophagic molecules depending on specific proteolysis could explain their pro-survival and pro-cell death functions. A detailed structure–function analysis of the autophagic molecules may further unravel their Jekyll and Hyde function in life and death.

Beclin 1 and its Role in Pathophysiology

Although we need to broaden our autophagy-centric view, the role of Beclin 1 in pathophysiology has been so far correlated only to its function in autophagy, for example, the removal of misfolded proteins and protein aggregates, and the elimination of invading pathogens. Beclin 1 is linked to several disorders, including cancer, cystic fibrosis, neurodegenerative diseases, and infectious diseases. **Table 2** gives an overview of disorders that might be linked to Beclin 1 malfunction (for a more extended review we refer to ref. 118). Most of these diseases are associated with altered Beclin 1 levels. In addition, Beclin 1 can be sequestered in protein aggregates or held in check by inhibitory interactions. Beclin 1-dependent autophagy has been implicated in the elimination of pathogens, including bacteria and viruses. Group A *Streptococcus* (GAS) infections, for example, result in the dissociation of NLRP4 from Beclin 1, allowing Beclin 1 to initiate a bactericidal autophagic response.[47] Whether these bacteria possess particular virulence factors to counteract their autophagic destruction is currently unknown. However, several viruses target Beclin 1 as a strategy to accomplish their infective life cycle. Herpes simplex virus (HSV-I), which causes lethal encephalitis in mice, has developed a strategy to increase its virulence by the binding of its neurovirulence factor, ICP34.5, to host Beclin 1, thereby inhibiting Beclin 1-dependent autophagy.[62,63] Similarly, the interaction of HIV Nef with Beclin 1 enhances the yield of infectious HIV.[60] These data support a role for Beclin 1 in the prevention of infectious diseases.

In cystic fibrosis, sustained transglutaminase activity causes Beclin 1 crosslinking and its subsequent sequestration in inclusion bodies. This prevents Beclin 1 from fulfilling its autophagic function.[106,112] Beclin 1 levels are modified also in neurodegenerative diseases, which are extensively linked to autophagy. In the brain of patients with Alzheimer disease, for example, Beclin 1 is depleted due to caspase-mediated proteolysis.[107] However, the most striking link to human pathology is Beclin 1's function in tumorigenesis. The *BECN1* gene maps, on chromosome 17q21, to a tumor susceptibility locus commonly deleted in breast, ovarian and prostate cancer.[46] Allelic deletion of *BECN1* is frequently found in carcinoma cell lines, and Beclin 1 expression is reduced in breast, ovarian and brain tumors.[44,76,78,114] In addition, Beclin 1 expression in the human breast carcinoma cell line MCF-7 inhibits in vitro clonigenicity and tumorigenesis in nude mice.[16] Moreover, *Beclin 1*$^{+/-}$ mice have a high incidence of spontaneous tumors, including lymphoma and liver and lung cancer. These data classify Beclin 1 as a haplo-insufficient tumor suppressor.[17,18,46] Rarely, somatic mutations in the *BECN1* coding region are discovered in human cancers.[119] But the functional effects of these mutations are negligible and they probably do not contribute to the pathogenesis of the cancers. Recently, epigenetic

silencing of *BECN1* was found to result in reduced Beclin 1 protein levels in sporadic breast tumors, and one group reported loss of heterozygosity of *BECN1* in 45% of the breast carcinoma tissues they examined.[76,119] Because of the central role of Beclin 1 in autophagy regulation, tumorigenesis in *Beclin 1*$^{+/-}$ mice was initially fully ascribed to the lack of autophagic activity. But one must keep in mind the dual role of autophagy in cancer.[120] On the one hand, autophagy, as a cleanup mechanism, limits accumulation of harmful proteins, damaged organelles and genome damage, and consequently prevents malignant transformation and cancer progression. On the other hand, its pro-survival role under non-optimal growth conditions can provide the established tumor with a mechanism that promotes its survival in a nutrient poor and hypoxic microenvironment. In line with this, some reports demonstrate an increase rather than decrease in Beclin 1 expression in human gastric and colorectal tumors.[117] However, Beclin 1 fulfills other, non-autophagy-related functions that could also contribute to its tumor-modulating properties. For example, Beclin 1 is implicated in receptor degradation and cytokinesis.[29] Downregulation of receptor degradation could result in excessive mitogenic signaling, and incomplete cell division could cause aneuploidy.[121,122] In addition, the apparent role of Beclin 1 in multiple membrane trafficking processes could link its dysfunction to many human diseases.

Concluding Remarks

Beclin 1 is a multifaceted protein. Because it acts as a key scaffold for the assembly of distinct signaling complexes, it is crucial in several pathways in all eukaryotic species. Beclin 1 governs most autophagy processes and is implicated in endocytic trafficking, phagocytosis, cytokinesis control and pollen germination. All of these are non-autophagy functions, but they all involve membrane flux and the corresponding controls. Consequently, Beclin 1 is involved in many biological processes, including development, differentiation, stress adaptation, inflammation, tumorigenesis, aging, and cell death. Indeed, the central role of Beclin 1 in cellular and organism function is emphasized by the wealth of diseases associated with Beclin 1 malfunction or deficiency, and, therefore, Beclin 1 is considered a valuable target for treatment of distinct pathologies and cancer. Beclin 1 expression levels can determine the autophagy response, which ameliorates disease symptoms, extends mean life span, and improves the efficacy of several anti-cancer drugs. Much insight has been gained over the last few years into how the Beclin 1 scaffolding function is regulated, and this information is crucial for the ability to manipulate Beclin 1-dependent autophagy or its non-autophagy functions. It is clear that the expression levels of Beclin 1 are tightly controlled, and in addition, the research field has advanced a lot in understanding the regulation of Beclin 1 by its interaction with Bcl-2. In turn, this interaction is fine-tuned by post-translational modifications, and more precisely, by phosphorylation and ubiquitination. Also, some of the enzymes participating in these modifications have been identified, and future findings can generate a more detailed picture. In addition, ongoing research is focusing on how Beclin 1 is directly implicated in the modulation of cell death, and this can lead to the understanding of the physiological significance of this role. Eventually, these new insights will lead to the design of novel, promising therapeutic interventions.

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