HHS Public Access

Author manuscript

Neuroscience. Author manuscript; available in PMC 2024 May 10.

Published in final edited form as:

Neuroscience. 2023 May 10; 518: 4–9. doi:10.1016/j.neuroscience.2022.05.002.

Commentary: BAG3 as a mediator of endosome function and tau clearance

Heng Lin,

Carol A. Deaton,

Gail V. W. Johnson*

Department of Anesthesiology and Perioperative Medicine, University of Rochester, 601 Elmwood Ave, Box 604, Rochester, NY 14642 USA

Abstract

Tauopathies are a group of heterogeneous neurodegenerative conditions characterized by the deposition of abnormal tau protein in the brain. The underlying mechanisms that contribute to the accumulation of tau in these neurodegenerative diseases are multifactorial; nonetheless, there is a growing awareness that dysfunction of endosome-lysosome pathways is a pivotal factor. BCL2 associated athanogene 3 (BAG3) is a multidomain protein that plays a key role in maintaining neuronal proteostasis. Further, recent data indicate that BAG3 plays an important role in mediating vacuolar-dependent degradation of tau. Overexpression of BAG3 in a tauopathy mouse model decreased pathological tau levels and alleviated synapse loss. High throughput screens of BAG3 interactors have identified key players in the vacuolar system; these include clathrin and regulators of small GTPases. These findings suggest that BAG3 is an important regulator of endocytic pathways. In this commentary, we discuss the potential mechanisms by which BAG3 regulates the vacuolar system and tau proteostasis.

Introduction

The microtubule associated protein tau is an evolutionarily conserved protein that, among other functions (Tapia-Rojas et al., 2019), modulates the dynamics of microtubules in neuronal axons (Qiang et al., 2018). Tauopathies are a group of heterogeneous neurodegenerative conditions characterized by the deposition of abnormal tau protein in the brain. Although the underlying mechanisms that contribute to the aberrant accumulation of the tau protein have not been fully defined, there is compelling data indicating that impaired processing mechanisms are likely a factor. Therefore, elucidating the molecular events that mediate tau clearance is essential for understanding the mechanisms underlying tauopathies.

*Correspondence should be addressed to: Gail V.W. Johnson, PhD, Department of Anesthesiology and Perioperative Medicine, University of Rochester, 601 Elmwood Ave, Box 604, Rochester, NY 14642, gail_johnsonvoll@urmc.rochester.edu, +1-585-276-3740 (voice).

The vacuolar system plays an essential role in neurons as it is used to orchestrate the uptake, sorting, trafficking, degradation, and release of tau. This system includes endocytosis for tau uptake, exosomes for tau release, and the endosome-lysosome system for tau trafficking and degradation (Brunello et al., 2020;Grant and Donaldson, 2009;Nixon et al., 2000;Yan and Zheng, 2021). Of note, dysregulation of the vacuolar systems occurs early in the pathogenesis of Alzheimer's disease (AD) and other neurodegenerative diseases (Kimura and Yanagisawa, 2018;Nixon, 2005). Indeed, defects in the lysosomal membrane concomitant with the accumulation of autophagosomes, lysosomes, and multi-vesicular bodies (MVBs) have been reported in numerous tauopathies including Corticobasal Degeneration (CBD) (Piras et al., 2016;Puangmalai et al., 2020), and Progressive Supranuclear Palsy (PSP)(Jiang and Bhaskar, 2020), as well as AD (Cataldo et al., 2004;Nixon, 2005). Conversely, fragmented tau can impair chaperone-mediated autophagy (CMA) and lysosomal function, which could lead to enhanced tau oligomerization and aggregation (Wang et al., 2009). Further, genome-wide association studies have identified a number of genes related to AD susceptibility including: BIN1, PICALM, CD2AP, RIN3, SORL1, GRN, and PLD3, which modulate the endosome-lysosome and autophagy pathways (Bertram and Tanzi, 2009;Kamboh et al., 2012). Finally, a recent study that analyzed snRNA data bases from human excitatory and inhibitory neurons found that the protein Bcl-2-associated anthogene 3 (BAG3) was expressed to a significantly greater extent in neurons that were resistant to developing tau accumulations compared to neurons vulnerable to developing tau aggregates (Fu et al., 2019). Indeed, BAG3 likely plays a key role in regulating vacuolar processes that mediate tau clearance, which has been an active area of investigation in our lab for the past decade.

BAG3

BAG3 is a stress-induced, multi-domain protein with expression levels that rise with aging potentially reflecting the critical role of BAG3 in maintaining proteostasis and neuronal health (Klimek et al., 2017;Lin et al., 2021). The expression of BAG3 shows an interesting bi-phasic pattern during the development of the rat central nervous system. In the embryonic stage, BAG3 expression increases in the cortical and hippocampal neurons during development. These increases in BAG3 continue into the first postnatal week and then decline thereafter, suggesting BAG3 plays a role in regulating neuronal development (Choi et al., 2006). Subsequently, BAG3 expression increases in the mouse hippocampus from 4 to 12 months of age, which indicates BAG3 may also play a role in maintaining protein homeostasis during aging and that dysregulation could be a contributing factor in age-related neurodegenerative conditions (Tang et al., 2018). Indeed, data indicate that BAG3 levels are significantly lower in AD cases compared to age matched controls (Zhou et al., 2020).

Our lab was the first to demonstrate a role for BAG3 in clearing tau species in neurons (Lei et al., 2015). Proteasome inhibition increased BAG3 expression and promoted phosphorylated tau clearance in neurons, and knockdown of BAG3 attenuated autophagy measures and increased the accumulation of phosphorylated tau in neurons (Lei, et al., 2015). We also showed that BAG3 regulates autophagic flux in the neurites through interaction with the post-synaptic cytoskeleton protein synaptopodin (Ji et al., 2019). In our recent study, we investigated the endogenous neuronal BAG3 interactome through

unbiased immunoprecipitation-coupled mass spectrometry (IP-MS). Surprisingly, among the BAG3-interacting proteins, the endosome-lysosome pathway was the most over-represented. These interactors were in three major categories including: GTPase pathways (IQSEC3, GAPVD1, TBC1D10B), clathrin (CLTC, DNM2, AP2B1), and the cytoskeleton (Tubb3, Tubb2a, Tubb4b, Actb, Capzb, Capza2). In this review, we will review our own findings and those of others which shed light on how BAG3 can mediate tau processing by regulating the vacuolar system (Lin et al., 2022).

Mechanisms of tau entry into the vacuolar system varies depending on the localization of tau. Endocytosis is considered one of the major pathways for the entrance of extracellular tau into the vacuole system (Evans et al., 2018;Zhao et al., 2021). Intracellular tau likely enters the vacuolar system through endosomal sorting complexes required for transport (ESCRT)-mediated or autophagy pathways (Lin, et al., 2021). Here, we will focus on the potential involvement of BAG3 in regulating tau's entrance into the vacuolar system which either occurs primarily through the ESCRT pathway for intracellular tau or occurs via clathrin-mediated endocytosis (CME) for extracellular tau. For a recent review on the role of BAG3 in mediating autophagy-dependent tau clearance, see Ji et al (Ji et al., 2022).

BAG3 regulates Rab35 and ESCRT-dependent entry of intracellular tau into the vacuole system

There is a growing awareness that the ESCRT pathway plays an important role in directing intracellular tau into the vacuolar system (Chen et al., 2019;Vaz-Silva et al., 2018). ESCRT regulates the formation and scission of vesicles that bud away from the cytosol into the internal vacuolar system or out of the cells (Schoneberg et al., 2017). The core ESCRT machinery is made up of three subcomplexes; ESCRT- I, ESCRT-II, and ESCRT-III. ESCRT-I (TSG101, VPS28, VPS37 and MVB12 or UBAP1) interacts with ESCRT-II (EAP45, EAP30 and EAP20) through VPS28 and EAP45. ESCRT-III (CHMP2 to CHMP6), which is recruited by ESCRT-II, collaborates with the ATPase, VPS4, to promote the constriction and scission of membrane (Vietri et al., 2020). The ESCRT-0 complex (Hrs and STAM) interacts with both ubiquitylated and non-ubiquitylated proteins to target them to the endosome (Pridgeon et al., 2009;Yamashita et al., 2008). ESCRT-0 is recruited to the endosomal membrane by phosphatidylinositol 3-phosphate, and clusters into microdomains via clathrin binding (Migliano and Teis, 2018). ESCRT-0 then recruits in ESCRT-I, leading to the assembly of the ESCRT machinery and internalization of captured cargos into the endosome (Bache et al., 2003;Katzmann et al., 2003). ESCRT plays an important role in multiple cellular process including endosome maturation, membrane repair, and many other processes (Gatta and Carlton, 2019). Recent studies have provided evidence that BAG3 modulates the ESCRT pathway, as it associates with key proteins that regulate ESCRT function (Lin, et al., 2021). Further, in a study of the human binary protein interactome, BAG3 was found associated with an ESCRT-I core protein, VPS37, and ESCRT-III protein, CHMP4C, (Luck et al., 2020).

The regulation of Rabs and other small GTPases plays a key role in coordinating the functions of the ESCRT pathway (Kumar et al., 2019;Lumb et al., 2011;Sheehan et al.,

2016). BAG3 interacts with and regulates the primary GTPase activating protein (GAP) for Rab35, TBC1D10B (Hsu et al., 2010;Lin, et al., 2021). Rab35 plays an essential role in mediating Hrs-dependent targeting of clients, including tau, to the endosome (Vaz-Silva, et al., 2018). The interaction of BAG3 withTBC1D10B prevents it from inactivating Rab35, thus keeping it in the active GTP bound state. Reduction of BAG3 levels results in lower Rab35 activity (Lin, et al., 2021). Rab35 plays a critical role in initiating recruitment of cargos to the ESCRT system (Klinkert and Echard, 2016;Sheehan, et al., 2016); thus, BAG3 facilitates this process by sequestering TBC1D10B and preventing it from promoting the conversion of Rab35-GTP to Rab35-GDP (Hsu, et al., 2010). Further, the mobility of Hrs and its association with Rab35 are increased by the presence of BAG3, whereas loss of BAG3 decreases Hrs and Rab35 interactions (Lin, et al., 2021). Phospho-tau is one cargo that is directed to endo-lysosomal degradation through the ESCRT system (Chen, et al., 2019;Vaz-Silva, et al., 2018), and thus the modulation of the ESCRT system by BAG3 plays an important role in regulating the degradation of phosphorylated tau through this pathway (Lin, et al., 2021). Indeed, reduction of BAG3 increases the accumulation of phosphorylated tau, whereas depletion of TBC1D10B decreases the level of phosphorylated tau in neurons (Lin, et al., 2021). Consistent with the notion that the BAG3/TBC1D10B association helps regulate tau sorting into ESCRT system, BAG3 knockdown decreases colocalization between phospho-tau and CHMP2B, an ESCRT-III component. Furthermore depletion of TBC1D10B alone or depletion of both BAG3 and TBC1D10B increases the localization of phospho-tau to the ESCRT system (Lin, et al., 2021). Overall, these findings show that BAG3 regulates the recruitment of ESCRT-0/Hrs to the endosome, in part by interacting withTBC1D10B to attenuate the inactivation of Rab35. Increases in Rab35 activity lead to the enhanced recruitment of Hrs-associated tau to Rab35. This mechanism leads to the internalization of intracellular tau into endosomes for trafficking to lysosomes and degradation (Vaz-Silva, et al., 2018).

Another key interactor of BAG3 that we identified was, IQSEC3, a guanine nucleotide exchange factor (GEF) for Arf6 (Shoubridge et al., 2010). Arf6 is a small GTPase that localizes preferentially in inhibitory post-synapses (Fukaya et al., 2011). The Arf6-GEF activity of IQSEC3 is required for maintenance of GABAergic synapse structure, raising the possibility that normal levels of Arf6 activity are crucial for GABAergic synapse development and maintenance (Sannerud et al., 2011). Arf6 has been reported to play an important role in axonal outgrowth, dendritic branching, and spine formation in primary cultured cortical and hippocampal neurons (Jaworski, 2007). Recent studies have found that Arf6 may play a role in tauopathy. Overexpression of wild-type Arf6 in HEK cells strongly enhances tau secretion, which is effectively blocked by Arf6 siRNA (Yan et al., 2016). In addition, Arf6 mediates the trafficking of BACE1 to the early endosomal compartment and thus the processing of the amyloid protein precursor protein (APP) to form Aβ. Inactivation of Arf6 blocks the recycling of cargo proteins from the endosome to the cell surface and allows BACE1 and APP to reside longer in the endosomal processing compartment. This increases APP processing and consequently enhances Aβ production, which could contribute to the development of tau pathology (Reiss et al., 2018;Sannerud, et al., 2011).

Interestingly, Arf6 has an antagonistic relationship with Rab35. For instance, Arf6 activity is negatively regulated by ACAP2, which is a Rab35 effector and an Arf6 GAP. Conversely,

Arf6 recruits the Rab35 GAP, TBCB1D10B, to clathrin-coated structures to control the activity of Rab35 and its loading into clathrin-coated structures (Chesneau et al., 2012). In addition, Arf6 stimulates clathrin/AP-2 recruitment to synaptic membranes (Krauss et al., 2003). Because BAG3 interacts with both a GAP for Rab35 (TBC1D10B) and a GEF for Arf6 (IQSEC3), it may be a crucial factor in mediating the relationship of these two key small GTPases.

BAG3 also associates with the clathrin heavy chain, which is involved in the maturation of the endosome. Interestingly, clathrin and Hrs collaborate to regulate intraluminal vesicle (ILV) formation. Hrs recruits clathrin to early endosomes (Raiborg et al., 2001), and then clathrin promotes ESCRT-0 disassembly, allowing for ESCRT-mediated formation of the ILV (Norris et al., 2017;Raiborg et al., 2006). Interestingly, HSC70, which also binds BAG3, participates in the disassembly of endosomal clathrin and ESCRT-0 (Norris, et al., 2017). Live cell imaging showed that formation of MVBs is mediated by characteristic, repetitive, and concerted recruitment waves of the entire ESCRT machinery to endosomes, starting immediately after cargo internalization. The highly coordinated recruitment of ESCRT machinery can ensure that the cargo, which is sequestered by ESCRT-0, will be efficiently sorted into forming ILVs (Wenzel et al., 2018).

Because BAG3 interacts with components that regulate the ESCRT system, we hypothesize that BAG3 plays a key role in mediating the endocytic pathway to control tau's entrance into vacuolar system. We speculate that BAG3, by interacting with key players including clathrin, TBC1D10B, IQSEC3, and other mediators of the ESCRT machinery, coordinates this highly dynamic process (Figure 1). In this pathway, BAG3 interacts with IQSEC3 which activates Arf6. The activated Arf6 recruits clathrin to the endosome membrane, and TBC1D10B is recruited to the clathrin-coated structures. BAG3 interacts with both clathrin heavy chains and TBC1D10B. TBC1D10B is a GAP that inactivates Rab35, and this process is controlled by BAG3. The activated Rab35 can inactivate Arf6 through ACAP2. The activated Rab35 will then recruit Hrs (ESCRT-0) which binds tau and further recruits clathrin and other ESCRT machinery to the endosome membrane. The recruitment of ESCRT machinery can ensure that tau, which is sequestered by ESCRT-0, will be efficiently sorted into the forming ILV. The recruited clathrin will dissociate Hrs, which makes it possible to form other ILVs. During this process, BAG3 directly interacts with TBC1D10B to prevent inactivation of Rab35. Moreover, BAG3 interacts with other ESCRT machinery components including VPS37 (ESCRT-1) and CHMP4 (ESCRT-III) (Gatta and Carlton, 2019;Lin, et al., 2021). This evidence indicates that BAG3 may act as a key regulator in fine tuning the ESCRT system to regulate tau's entrance into the vacuolar system.

Summary

It is well-established that endosome-lysosome pathway dysfunction is a significant contributor to the pathogenesis of AD and other neurodegenerative diseases (Nixon, 2005;Pensalfini et al., 2020). Further, there is an increasing awareness of the importance of this pathway in tauopathies, as deficits in the vacuolar system occur early and precede the accumulation of tau (Nixon, 2005;Pensalfini, et al., 2020). Previous studies have established that BAG3 is an autophagy regulator (Klimek, et al., 2017;Sturner and Behl,

2017). Recently, several unbiased IP-MS analyses examining BAG3 interactors demonstrate its close relationship with endosome-lysosome pathways (Hiebel et al., 2020;Lin, et al., 2021). These and other data strongly indicate that BAG3 regulates a broad range of vacuolar system events, beyond its well-studied role in autophagic processes (Behl, 2016;Ji, et al., 2019;Klimek, et al., 2017), indicating its role in facilitating tau degradation and preventing tau propagation. Indeed, human brains with higher levels of BAG3 in specific neuronal populations exhibit a resistance to developing tau pathology (Fu, et al., 2019). The ability of BAG3 to protect against tau accumulation in human cases is further supported by data demonstrating that BAG3 promotes tau clearance in cultured neurons as well as in tauopathy mouse models. Importantly, overexpression of BAG3 in tauopathy mouse models alleviates the synaptic loss (Lin, et al., 2021). These findings support the conceptual framework that BAG3 is a key regulator of vacuolar system and, thus, an important factor in the development of tau pathology.

Future studies

Based on the IP-MS data, neuronal BAG3 interacts with a group of proteins involved in CME including the heavy chain of clathrin, AP2 complex subunits, and dynamin. Our findings in neurons are also supported by a recent BAG3 proteomic study in HEK cells (Hiebel, et al., 2020). These findings clearly indicate a potential role for BAG3 in regulating CME. Future studies are needed to define the mechanisms by which BAG3 mediates CME. Another important area of study is the interaction of BAG3 with chaperone proteins, as the field would benefit from better understanding of how particular chaperone proteins can regulate the function of BAG3 in different vacuolar pathways. For example, the interaction of BAG3 with HSP70 through its BAG domain dramatically increases its ability to bind to and regulate TBC1D10B (Lin, et al., 2021). Indeed, approximately one third of the pathogenic mutations in BAG3 that cause myopathies occur in the α2 and α3 helix of the BAG domain which can impact the binding of HSP70 to BAG3 (Lin, et al., 2022). Further, our preliminary data indicate that the binding of BAG3 with IQSEC3 and GAPVD1 (a GEF for Rab5) (Hunker et al., 2006) are strongly increased when HSP70 is bound to BAG3. These findings indicate that BAG3 likely needs to interact with HSP70 to regulate the activity of proteins that regulate small GTPases (TBC1D10B, IQSEC3 and GAPVD1). Additionally, our in vitro protein binding assay showed that HSP70 doesn't directly bind with TBC1D10B, but may need interact with BAG3 to associate with TBC1D10B. Future studies are needed to define how HSP70's binding to BAG3 mediates its interaction with these GTPase regulators. How BAG3 impacts Arf6 and Rab5 activity and, thus, tau clearance through these pathways also needs further investigation. Indeed, overactivation of Rab5 has been shown to result in an AD-like phenotype, including the accumulation of phosphorylated tau (Pensalfini, et al., 2020). Overall, future studies to delineate the mechanisms by which BAG3 mediates vacuolar processes will significantly contribute to our understanding of the molecular mechanisms underlying tauopathies.

Acknowledgements

This work was supported by the National Institutes of Health (NIH) (Grant Nos. R56 AG067739, R01 NS098769, and R01 AG073121 [to GVWJ]). This work was also supported by Alzheimer's Association Grant (Grant ID AARF-21-721039 [to HL]).

References

Bache KG, Raiborg C, Mehlum A, Stenmark H (2003), STAM and Hrs are subunits of a multivalent ubiquitin-binding complex on early endosomes. J Biol Chem 278:12513–12521. [PubMed: 12551915]

Behl C (2016), Breaking BAG: The Co-Chaperone BAG3 in Health and Disease. Trends Pharmacol Sci 37:672–688. [PubMed: 27162137]

Bertram L, Tanzi RE (2009), Genome-wide association studies in Alzheimer's disease. Hum Mol Genet 18:R137–145. [PubMed: 19808789]

Brunello CA, Merezhko M, Uronen RL, Huttunen HJ (2020), Mechanisms of secretion and spreading of pathological tau protein. Cell Mol Life Sci 77:1721–1744. [PubMed: 31667556]

Cataldo AM, Petanceska S, Terio NB, Peterhoff CM, Durham R, Mercken M, Mehta PD, Buxbaum J, et al. (2004), Abeta localization in abnormal endosomes: association with earliest Abeta elevations in AD and Down syndrome. Neurobiol Aging 25:1263–1272. [PubMed: 15465622]

Chen JJ, Nathaniel DL, Raghavan P, Nelson M, Tian R, Tse E, Hong JY, See SK, et al. (2019), Compromised function of the ESCRT pathway promotes endolysosomal escape of tau seeds and propagation of tau aggregation. J Biol Chem 294:18952–18966. [PubMed: 31578281]

Chesneau L, Dambournet D, Machicoane M, Kouranti I, Fukuda M, Goud B, Echard A (2012), An ARF6/Rab35 GTPase cascade for endocytic recycling and successful cytokinesis. Curr Biol 22:147–153. [PubMed: 22226746]

Choi JS, Lee JH, Kim HY, Chun MH, Chung JW, Lee MY (2006), Developmental expression of Bis protein in the cerebral cortex and hippocampus of rats. Brain Res 1092:69–78. [PubMed: 16690035]

Evans LD, Wassmer T, Fraser G, Smith J, Perkinton M, Billinton A, Livesey FJ (2018), Extracellular Monomeric and Aggregated Tau Efficiently Enter Human Neurons through Overlapping but Distinct Pathways. Cell Rep 22:3612–3624. [PubMed: 29590627]

Fu H, Possenti A, Freer R, Nakano Y, Hernandez Villegas NC, Tang M, Cauhy PVM, Lassus BA, et al. (2019), A tau homeostasis signature is linked with the cellular and regional vulnerability of excitatory neurons to tau pathology. Nat Neurosci 22:47–56. [PubMed: 30559469]

Fukaya M, Kamata A, Hara Y, Tamaki H, Katsumata O, Ito N, Takeda S, Hata Y, et al. (2011), SynArfGEF is a guanine nucleotide exchange factor for Arf6 and localizes preferentially at post-synaptic specializations of inhibitory synapses. J Neurochem 116:1122–1137. [PubMed: 21198641]

Gatta AT, Carlton JG (2019), The ESCRT-machinery: closing holes and expanding roles. Curr Opin Cell Biol 59:121–132. [PubMed: 31132588]

Grant BD, Donaldson JG (2009), Pathways and mechanisms of endocytic recycling. Nat Rev Mol Cell Biol 10:597–608. [PubMed: 19696797]

Hiebel C, Sturner E, Hoffmeister M, Tascher G, Schwarz M, Nagel H, Behrends C, Munch C, et al. (2020), BAG3 Proteomic Signature under Proteostasis Stress. Cells 9.

Hsu C, Morohashi Y, Yoshimura S, Manrique-Hoyos N, Jung S, Lauterbach MA, Bakhti M, Gronborg M, et al. (2010), Regulation of exosome secretion by Rab35 and its GTPase-activating proteins TBC1D10A-C. J Cell Biol 189:223–232. [PubMed: 20404108]

Hunker CM, Galvis A, Kruk I, Giambini H, Veisaga ML, Barbieri MA (2006), Rab5-activating protein 6, a novel endosomal protein with a role in endocytosis. Biochem Biophys Res Commun 340:967–975. [PubMed: 16410077]

Jaworski J (2007), ARF6 in the nervous system. Eur J Cell Biol 86:513–524. [PubMed: 17559968]

Ji C, Lin H, Johnson GVW (2022), Chapter 8: BAG3 promotes tau clearance by regulating autophagy and other vacuolar-dependent degradative processes. In: Autophagy Dysfunction in Alzheimer's Disease and Dementia (Tadanori H, Tatsuro M, eds). Elsevier.

Ji C, Tang M, Zeidler C, Hohfeld J, Johnson GV (2019), BAG3 and SYNPO (synaptopodin) facilitate phospho-MAPT/Tau degradation via autophagy in neuronal processes. Autophagy 15:1199–1213. [PubMed: 30744518]

Jiang S, Bhaskar K (2020), Degradation and Transmission of Tau by Autophagic-Endolysosomal Networks and Potential Therapeutic Targets for Tauopathy. Front Mol Neurosci 13:586731. [PubMed: 33177989]

Kamboh MI, Demirci FY, Wang X, Minster RL, Carrasquillo MM, Pankratz VS, Younkin SG, Saykin AJ, et al. (2012), Genome-wide association study of Alzheimer's disease. Transl Psychiatry 2:e117. [PubMed: 22832961]

Katzmann DJ, Stefan CJ, Babst M, Emr SD (2003), Vps27 recruits ESCRT machinery to endosomes during MVB sorting. J Cell Biol 162:413–423. [PubMed: 12900393]

Kimura N, Yanagisawa K (2018), Traffic jam hypothesis: Relationship between endocytic dysfunction and Alzheimer's disease. Neurochem Int 119:35–41. [PubMed: 28697973]

Klimek C, Kathage B, Wordehoff J, Hohfeld J (2017), BAG3-mediated proteostasis at a glance. J Cell Sci 130:2781–2788. [PubMed: 28808089]

Klinkert K, Echard A (2016), Rab35 GTPase: A Central Regulator of Phosphoinositides and F-actin in Endocytic Recycling and Beyond. Traffic 17:1063–1077. [PubMed: 27329675]

Krauss M, Kinuta M, Wenk MR, De Camilli P, Takei K, Haucke V (2003), ARF6 stimulates clathrin/AP-2 recruitment to synaptic membranes by activating phosphatidylinositol phosphate kinase type Igamma. J Cell Biol 162:113–124. [PubMed: 12847086]

Kumar H, Pushpa K, Kumari A, Verma K, Pergu R, Mylavarapu SVS (2019), The exocyst complex and Rab5 are required for abscission by localizing ESCRT III subunits to the cytokinetic bridge. J Cell Sci 132.

Lei Z, Brizzee C, Johnson GV (2015), BAG3 facilitates the clearance of endogenous tau in primary neurons. Neurobiol Aging 36:241–248. [PubMed: 25212465]

Lin H, Koren SA, Cvetojevic G, Girardi P, Johnson GVW (2022), The role of BAG3 in health and disease: A "Magic BAG of Tricks". J Cell Biochem 123:4–21. [PubMed: 33987872]

Lin H, Tang M, Ji C, Girardi P, Cvetojevic G, Chen D, Koren SA, Johnson GVW (2021), BAG3 Regulation of RAB35 Mediates the Endosomal Sorting Complexes Required for Transport/Endolysosome Pathway and Tau Clearance. Biol Psychiatry.

Luck K, Kim DK, Lambourne L, Spirohn K, Begg BE, Bian W, Brignall R, Cafarelli T, et al. (2020), A reference map of the human binary protein interactome. Nature 580:402–408. [PubMed: 32296183]

Lumb JH, Leung KF, Dubois KN, Field MC (2011), Rab28 function in trypanosomes: interactions with retromer and ESCRT pathways. J Cell Sci 124:3771–3783. [PubMed: 22100919]

Migliano SM, Teis D (2018), ESCRT and Membrane Protein Ubiquitination. Prog Mol Subcell Biol 57:107–135. [PubMed: 30097773]

Nixon RA (2005), Endosome function and dysfunction in Alzheimer's disease and other neurodegenerative diseases. Neurobiol Aging 26:373–382. [PubMed: 15639316]

Nixon RA, Cataldo AM, Mathews PM (2000), The endosomal-lysosomal system of neurons in Alzheimer's disease pathogenesis: a review. Neurochem Res 25:1161–1172. [PubMed: 11059790]

Norris A, Tammineni P, Wang S, Gerdes J, Murr A, Kwan KY, Cai Q, Grant BD (2017), SNX-1 and RME-8 oppose the assembly of HGRS-1/ESCRT-0 degradative microdomains on endosomes. Proc Natl Acad Sci U S A 114:E307–E316. [PubMed: 28053230]

Pensalfini A, Kim S, Subbanna S, Bleiwas C, Goulbourne CN, Stavrides PH, Jiang Y, Lee JH, et al. (2020), Endosomal Dysfunction Induced by Directly Overactivating Rab5 Recapitulates Prodromal and Neurodegenerative Features of Alzheimer's Disease. Cell Rep 33:108420. [PubMed: 33238112]

Piras A, Collin L, Gruninger F, Graff C, Ronnback A (2016), Autophagic and lysosomal defects in human tauopathies: analysis of post-mortem brain from patients with familial Alzheimer disease, corticobasal degeneration and progressive supranuclear palsy. Acta Neuropathol Commun 4:22. [PubMed: 26936765]

Pridgeon JW, Webber EA, Sha D, Li L, Chin LS (2009), Proteomic analysis reveals Hrs ubiquitin-interacting motif-mediated ubiquitin signaling in multiple cellular processes. FEBS J 276:118–131. [PubMed: 19019082]

Puangmalai N, Bhatt N, Montalbano M, Sengupta U, Gaikwad S, Ventura F, McAllen S, Ellsworth A, et al. (2020), Internalization mechanisms of brain-derived tau oligomers from patients with Alzheimer's disease, progressive supranuclear palsy and dementia with Lewy bodies. Cell Death Dis 11:314. [PubMed: 32366836]

Qiang L, Sun X, Austin TO, Muralidharan H, Jean DC, Liu M, Yu W, Baas PW (2018), Tau Does Not Stabilize Axonal Microtubules but Rather Enables Them to Have Long Labile Domains. Curr Biol 28:2181–2189 e2184. [PubMed: 30008334]

Raiborg C, Bache KG, Mehlum A, Stang E, Stenmark H (2001), Hrs recruits clathrin to early endosomes. EMBO J 20:5008–5021. [PubMed: 11532964]

Raiborg C, Wesche J, Malerod L, Stenmark H (2006), Flat clathrin coats on endosomes mediate degradative protein sorting by scaffolding Hrs in dynamic microdomains. J Cell Sci 119:2414–2424. [PubMed: 16720641]

Reiss AB, Arain HA, Stecker MM, Siegart NM, Kasselman LJ (2018), Amyloid toxicity in Alzheimer's disease. Rev Neurosci 29:613–627. [PubMed: 29447116]

Sannerud R, Declerck I, Peric A, Raemaekers T, Menendez G, Zhou L, Veerle B, Coen K, et al. (2011), ADP ribosylation factor 6 (ARF6) controls amyloid precursor protein (APP) processing by mediating the endosomal sorting of BACE1. Proc Natl Acad Sci U S A 108:E559–568. [PubMed: 21825135]

Schoneberg J, Lee IH, Iwasa JH, Hurley JH (2017), Reverse-topology membrane scission by the ESCRT proteins. Nat Rev Mol Cell Biol 18:5–17. [PubMed: 27703243]

Sheehan P, Zhu M, Beskow A, Vollmer C, Waites CL (2016), Activity-Dependent Degradation of Synaptic Vesicle Proteins Requires Rab35 and the ESCRT Pathway. J Neurosci 36:8668–8686. [PubMed: 27535913]

Shoubridge C, Walikonis RS, Gecz J, Harvey RJ (2010), Subtle functional defects in the Arf-specific guanine nucleotide exchange factor IQSEC2 cause non-syndromic X-linked intellectual disability. Small GTPases 1:98–103. [PubMed: 21686261]

Sturner E, Behl C (2017), The Role of the Multifunctional BAG3 Protein in Cellular Protein Quality Control and in Disease. Front Mol Neurosci 10:177. [PubMed: 28680391]

Tang M, Ji C, Pallo S, Rahman I, Johnson GVW (2018), Nrf2 mediates the expression of BAG3 and autophagy cargo adaptor proteins and tau clearance in an age-dependent manner. Neurobiol Aging 63:128–139. [PubMed: 29304346]

Tapia-Rojas C, Cabezas-Opazo F, Deaton CA, Vergara EH, Johnson GVW, Quintanilla RA (2019), It's all about tau. Prog Neurobiol 175:54–76. [PubMed: 30605723]

Vaz-Silva J, Gomes P, Jin Q, Zhu M, Zhuravleva V, Quintremil S, Meira T, Silva J, et al. (2018), Endolysosomal degradation of Tau and its role in glucocorticoid-driven hippocampal malfunction. EMBO J 37.

Vietri M, Radulovic M, Stenmark H (2020), The many functions of ESCRTs. Nat Rev Mol Cell Biol 21:25–42. [PubMed: 31705132]

Wang Y, Martinez-Vicente M, Kruger U, Kaushik S, Wong E, Mandelkow EM, Cuervo AM, Mandelkow E (2009), Tau fragmentation, aggregation and clearance: the dual role of lysosomal processing. Hum Mol Genet 18:4153–4170. [PubMed: 19654187]

Wenzel EM, Schultz SW, Schink KO, Pedersen NM, Nahse V, Carlson A, Brech A, Stenmark H, et al. (2018), Concerted ESCRT and clathrin recruitment waves define the timing and morphology of intraluminal vesicle formation. Nat Commun 9:2932. [PubMed: 30050131]

Yamashita Y, Kojima K, Tsukahara T, Agawa H, Yamada K, Amano Y, Kurotori N, Tanaka N, et al. (2008), Ubiquitin-independent binding of Hrs mediates endosomal sorting of the interleukin-2 receptor beta-chain. J Cell Sci 121:1727–1738. [PubMed: 18445679]

Yan M, Zheng T (2021), Role of the endolysosomal pathway and exosome release in tau propagation. Neurochem Int 145:104988. [PubMed: 33582164]

Yan X, Nykanen NP, Brunello CA, Haapasalo A, Hiltunen M, Uronen RL, Huttunen HJ (2016), FRMD4A-cytohesin signaling modulates the cellular release of tau. J Cell Sci 129:2003–2015. [PubMed: 27044754]

Zhao J, Wu H, Tang XQ (2021), Tau internalization: A complex step in tau propagation. Ageing Res Rev 67:101272. [PubMed: 33571704]

Zhou J, Chow HM, Liu Y, Wu D, Shi M, Li J, Wen L, Gao Y, et al. (2020), Cyclin-Dependent Kinase 5-Dependent BAG3 Degradation Modulates Synaptic Protein Turnover. Biol Psychiatry 87:756–769. [PubMed: 31955914]

Highlights

- BAG3 is a multidomain protein that plays a key role in maintaining neuronal proteostasis.
- BAG3 plays an important role in mediating vacuolar-dependent degradation of tau.
- In the BAG3 interactome, the endosome-lysosome pathway was the most over-represented.
- BAG3 regulates the recruitment of ESCRT-0/Hrs to the endosome, and thus tau, in part by interacting withTBC1D10B to attenuate the inactivation of Rab35.
- BAG3 is a key regulator of vacuolar system and, thus, an important factor in the development of tau pathology.

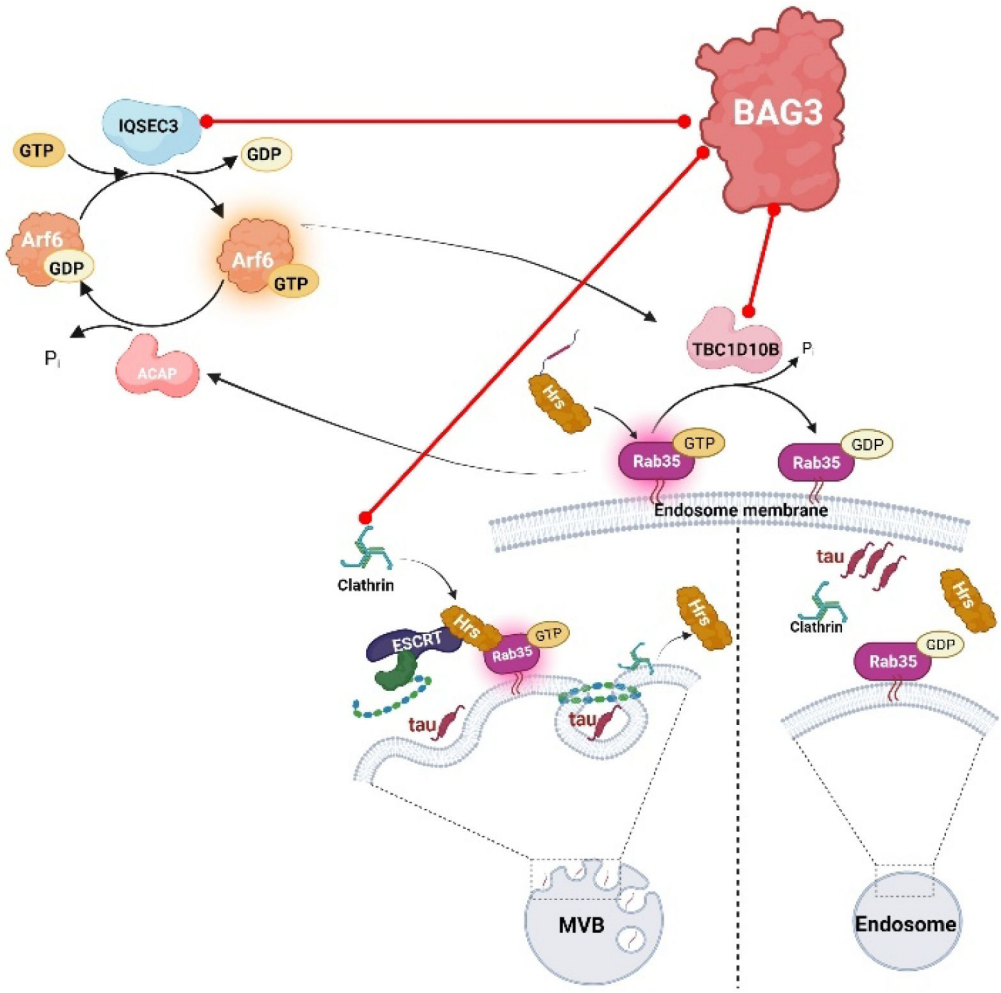

Figure 1. BAG3 interacts with clathrin, TBC1D10B and IQSEC3 to form a network regulating the endocytic pathway.

IQSEC3, a GEF, activates Arf6 promoting the GTP bounded state. Activated Arf6 recruits clathrin to the vacuolar membrane, and TBC1D10B is recruited to the clathrin-coated structures. TBC1D10B is a GAP that inactivates Rab35, and this process is controlled by BAG3. The activated Rab35 can inactivate Arf6 through ACAP2. The activated RAB35 will recruit the ESCRT-0 component, Hrs, which interacts with tau, and further recruit clathrin and other ESCRT machinery to endosome membrane. The recruitment of ESCRT machinery can ensure that the cargo, which is sequestered by ESCRT-0, will be efficiently sorted into forming one intraluminal vesicle (ILV). The recruited clathrin will dissociate from Hrs which allows it to proceed and promote the formation of the next ILV. During this process, BAG3 directly interacts with and sequestersTBC1D10B, attenuating its ability to inactivate Rab35. MVB, multivesicular body.