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REVIEW

p62/SQSTM1 – steering the cell through health and disease

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ABSTRACT

SQSTM1 (also known as p62) is a multifunctional stress-inducible scaffold protein involved in diverse cellular processes. Its functions are tightly regulated through an extensive pattern of post-translational modifications, and include the isolation of cargos degraded by autophagy, induction of the antioxidant response by the Keap1–Nrf2 system, as well as the regulation of endosomal trafficking, apoptosis and inflammation. Accordingly, malfunction of SQSTM1 is associated with a wide range of diseases, including bone and muscle disorders, neurodegenerative and metabolic diseases, and multiple forms of cancer. In this Review, we summarize current knowledge regarding regulation, post-translational modifications and functions of SQSTM1, as well as how they are dysregulated in various pathogenic contexts.

KEY WORDS: p62, Sqstm1, Selective autophagy, Phase separation, Keap1–Nrf2 system, Proteinopathies

Introduction

Sequestosome 1 (SQSTM1; also known as p62) is conserved in metazoans, and autophagy – the process with which SQSTM1 is primarily associated – is conserved throughout the eukaryotes (Reggiori and Klionsky, 2002; Svenning et al., 2011). In humans, *SQSTM1* is located on chromosome 5 and consists of eight exons that span 16 kb (Fig. 1A). *SQSTM1* is expressed in all tissues.

The SQSTM1 protein is a signaling adaptor containing a Phox1 and Bem1p (PB1) domain, a ZZ-type zinc finger (ZZ) domain, two nuclear localization signals (NLSs), a TRAF6-binding domain (TB), a nuclear export signal (NES), an LC3-interacting region (LIR), a Keap1-interacting region (KIR) and a ubiquitin-associated (UBA) domain (Fig. 1B). At the subcellular level, SQSTM1 is found not only in the cytoplasm but also in the nucleus, and on mitochondria, autophagosomes and lysosomes (Pankiv et al., 2010; Seibenhener et al., 2013).

Although SQSTM1 can be degraded by the proteasome (Aichem et al., 2012; Song et al., 2016) or through endosomal-related autophagy (Mejlvang et al., 2018) under certain circumstances, it is primarily degraded through selective autophagy. Accordingly, measuring its level has been a common method for monitoring autophagic flux (Ichimura and Komatsu, 2010; Yoshii and Mizushima, 2017).

In addition to its role in autophagy, SQSTM1 has been linked to other cellular processes, such as adipogenesis through its interaction with extracellular signal-regulated kinase 1 (ERK1; officially known as MAKPK3) (Lee et al., 2010), NF-κB signaling through atypical protein kinase C (PKC) (Puls et al., 1997; Sanchez et al., 1998), receptor-interacting protein 1 (RIP1) (Sanz et al., 1999) and tumor necrosis factor receptor-associated factor 6 (TRAF6) (Sanz et al., 2000), the antioxidative stress response through Keap1 (Komatsu et al., 2010), in apoptosis through caspase 8 (Jin et al., 2009), and nutrient sensing through interactions with the mechanistic target of rapamycin complex 1 (mTORC1) components regulatory-associated protein of mTOR (Rptor), and Ras-related GTP-binding proteins C and D (RRAGC and RRAGD, respectively; hereafter referred to as RagC/D) (Durán et al., 2011).

To participate in multiple cellular pathways and act as a signaling hub, SQSTM1 must undergo extensive post-translational modifications (PTMs) and participate in interactions that allow the fine-tuned regulation of its function (Fig. 1B). In this Review, we summarize our current knowledge about how PTMs affect the role of SQSTM1, as well as the effect the imbalance of SQSTM1 has in various pathological conditions.

Decoding the pattern – mapping the post-translational modifications involved in SQSTM1-mediated autophagy

Autophagy is a highly conserved process, in which a wide variety of cellular components are translocated to the lysosome for degradation. This process takes place under basal conditions as well as in response to different cellular stressors, such as nutrient deprivation, pathogen infection, hypoxia or cell damage (Dikic and Elazar, 2018). The substrates degraded by this machinery are correspondingly diverse, ranging from soluble components of the cytoplasm to protein aggregates, damaged organelles, lipid droplets and glycogen. The selection and isolation of these substrates is usually mediated by receptor proteins, such as SQSTM1 (see Box 1 for other autophagy receptors; see Dikic and Elazar, 2018, and Mizushima, 2018 for thorough reviews on the process).

To promote autophagy, SQSTM1 forms long PB1-linked helical filaments that induce nucleation of the autophagosome membrane owing to the interaction between SQSTM1 and MAP1LC3B (hereafter referred to as LC3B), a protein anchored to this membrane (Ciuffa et al., 2015). Next, ubiquitylated proteins are recruited to these filaments, fragmenting them into shorter and less compact forms that are engulfed by the nascent autophagosomal membrane (Bjørkøy et al., 2005; Ciuffa et al., 2015; Clausen et al., 2010; Ichimura et al., 2008). Finally, these large structures are degraded through autophagy, with their accumulation a typical hallmark of impaired autophagy (Eino et al., 2015; Komatsu et al., 2007).

When its activity as an autophagy receptor is not required, SQSTM1 is held inactive through homodimerization of its UBA domain, which prevents it from interacting with ubiquitin (Isogai et al., 2011; Long et al., 2010). Phosphorylation events play a crucial role in liberating the UBA domain from dimeric repression; in particular, phosphorylation of its serine residue 407 through ULK1 has been shown to facilitate the transition from dimer to monomer (Lim et al., 2015). This modification is followed by phosphorylation of SQSTM1 on serine 403 through ULK1, casein kinase 2 (CK2) or TANK-binding kinase 1 (TBK1), which enhances its binding to ubiquitin chains (Matsumoto et al., 2011; Pilli et al., 2012). Finally, the cargos are degraded by autophagy (Fan et al., 2010; Ichimura et al., 2013; Taguchi et al., 2012).

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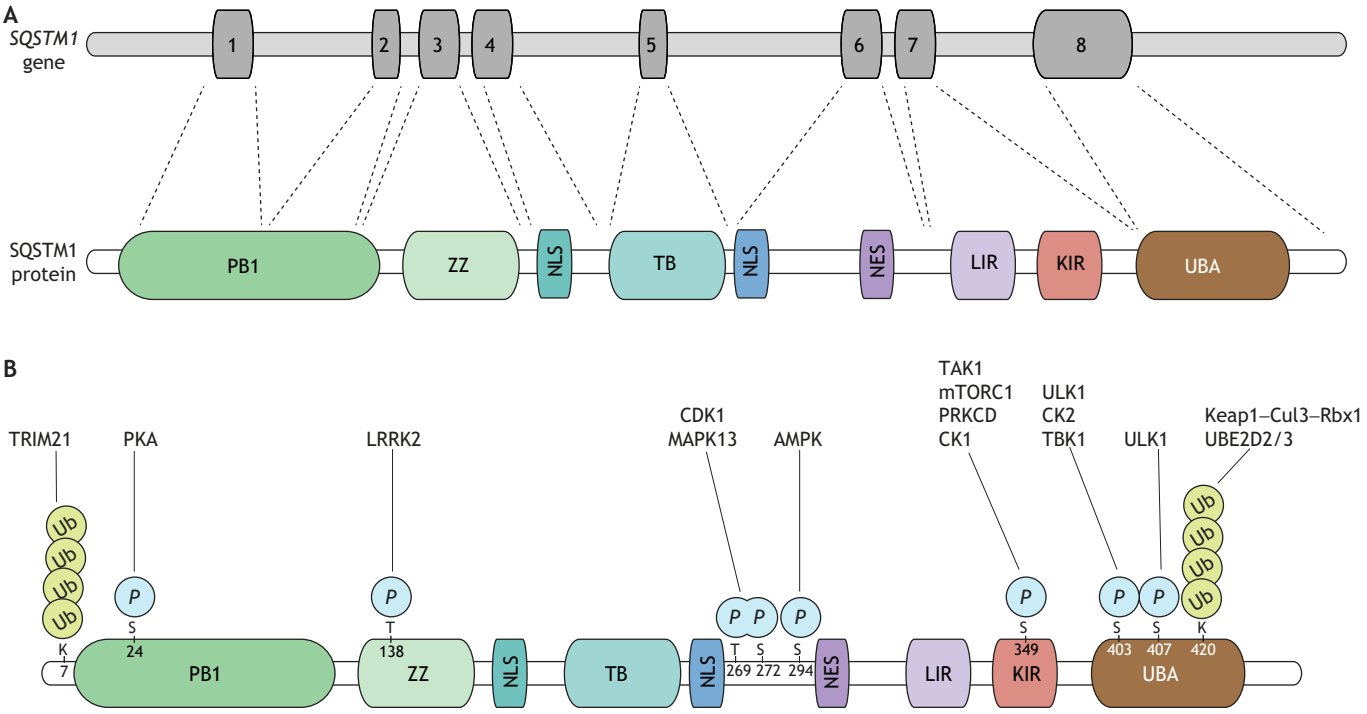

Fig. 1. (A) Gene structure of *SQSTM1*. Human *SQSTM1* is located on chromosome 5 (5q35.3). The 16-kb genomic locus encodes a 2870-ntd transcript containing eight exons. The equivalence between *SQSTM1* exons and protein domains is indicated by dashed lines. (B) Domain architecture of SQSTM1 and main post-translational modifications. The PB1 domain allows SQSTM1 to homo- or hetero-oligomerize with other PB1-containing proteins. Ubiquitylation of lysine residue 7 (K7) by TRIM21 and phosphorylation of serine residue 24 (S24) by PKA inhibit this oligomerization. Substrate recognition by the UBA domain is enhanced by phosphorylation of S403 by ULK1, CK2, or TBK1, phosphorylation of S407 by ULK1, and ubiquitylation of K420 by UBE2D2 or UBE2D3. Interaction with Keap1 is mediated through the KIR motif of SQSTM1 and enhanced through phosphorylation of S349 by mTORC1, CK1 (CSNK1A1), TAK1 or PRKCD, whereas ubiquitylation of residue K420 by the Keap1–Cul3–Rbx1 complex promotes autophagic degradation. AMPK-mediated phosphorylation of S294 in the linking region between the nuclear localization and export signals (NLS and NES, respectively), induces autophagic cell death, and phosphorylation of threonine 138 (T138) by LRRK2 contributes to neuronal cell death associated with Parkinson's disease. Phosphorylation of T269 and S272 is involved in either mTORC1-dependent autophagy inhibition or mitotic progression, depending on the kinase responsible for the modification (MAPK13 and CDK1, respectively). KIR, Keap1-interacting region; LIR, LC3-interacting region; NES, nuclear export signal; NLS, nuclear localization signal; PB1, Phox1 and Bem1p domain; TB, TRAF6-binding domain; Ub, ubiquitin; UBA, ubiquitin-associated domain; ZZ, ZZ-type zinc finger domain.

The Keap1–Cul3–Rbx1 complex has recently been shown to ubiquitylate lysine 420 in the UBA domain of SQSTM1, increasing its ability to recruit and degrade substrates by autophagy (Lee et al., 2017); the possible effects on the Keap1–Nrf2 antioxidant system are discussed below. SQSTM1 oligomerization and cargo degradation are further stimulated under conditions of oxidative stress through the formation of intermolecular disulfide bonds between cysteine 105 and 113 (Carroll et al., 2018). These bonds may reinforce PB1-dependent oligomerization to secure autophagic clearance in situations in which cellular homeostasis is compromised by oxidative stress (Carroll et al., 2018). Similarly, SQSTM1 forms disulfide bonds via cysteine 113 after recognition of N-terminally arginylated substrates by its ZZ domain (Cha-Molstad et al., 2018). These substrates of the so called N-end rule pathway are then degraded through autophagy in addition to their canonical proteasomal degradation (Cha-Molstad et al., 2017; Yoo et al., 2018).

Interestingly, perturbations in ubiquitin homeostasis, termed Ub stress, promote ubiquitylation of (at least) lysine 420 of SQSTM1 by the ubiquitin-conjugating enzymes E2 D2 and/or E2 D3 (UBE2D2 and/or UBE2D3, respectively), which allows SQSTM1 to bind to ubiquitylated cargos without its prior phosphorylation (Peng et al., 2017). In contrast, phosphorylation of SQSTM1 on serine 24 by protein kinase A (PKA) inhibits SQSTM1 oligomerization, thereby impairing its role in autophagy (Christian et al., 2014). SQSTM1 is also capable of suppressing autophagy in the presence of high levels of amino acids by promoting mTOR ubiquitylation, in collaboration with the E3 ubiquitin ligase TRAF6 and the mTORC1 subunits

Box 1. Selective autophagy is mediated by a several receptor proteins

There are two modes of autophagy: non-selective or selective autophagy in which the autophagosome randomly sequesters, respectively, cytoplasmic components or targets specific cargos. Selectivity of autophagy is ensured by two broad groups of receptor proteins, those of the ubiquitin-binding type and those of the trans-membrane type. The former are translocated onto specific autophagic cargos, such as damaged mitochondria and invasive microbes, when the cargos are ubiquitylated, whereas the latter directly localize on cargos and molecular markers, such as ubiquitin, are not needed. Most receptor proteins need LC3-interacting regions (LIRs) or GABARAP-interacting motifs (GIMs) to interact with LC3 or GABARAP family proteins. Through this interaction, autophagic cargos are selectively sequestered by autophagosome. To date, several receptor proteins have been identified: the ubiquitin-binding type (i.e. SQSTM1, NBR1, OPTN, TOLLIP, NDP52 and TAXBP1) and the trans-membrane type (i.e. NIX/BNIP3L, BNIP3, FUNDC1, FAM134B and CCPG1). The receptor proteins are not necessarily mutually exclusive, but rather act cooperatively. See Dikic and Elazar, 2018; Mizushima, 2018 for recent thorough reviews on the topic.

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Rptor and RagC/D (Durán et al., 2011; Linares et al., 2013). To achieve this autophagic inhibition under nutrient-rich conditions, prior phosphorylation of SQSTM1 at threonine 269 and serine 272 by MAPK13 (also known as p38-delta) appears to be required (Linares et al., 2015).

AMP-activated protein kinase (AMPK) is another master regulator of multiple cellular processes, including autophagy, and has been recently shown to phosphorylate SQSTM1 on serine 294 upon insulin withdrawal, thereby promoting mitophagy and autophagic cell death (Ha et al., 2017). Recent reports also propose that leucine-rich repeat kinase 2 (LRRK2), which has been associated with Parkinson's disease, directly phosphorylates SQSTM1 at threonine 138, and indirectly regulates its phosphorylation at serine 349 and 403 (Kalogeropulou et al., 2018), whereas SQSTM1 is known to promote autophagic degradation of LRRK2 (Park et al., 2016). These observations suggest a possible crosstalk between LRRK2- and SQSTM1-dependent pathways, which would be particularly relevant in the context of this neurodegenerative disease.

An additional link of SQSTM1 to Parkinson's pathology is suggested by the fact that parkin promotes the proteasomal degradation of SQSTM1 through its ubiquitylation (Song et al., 2016), which is in contrast with their collaborative role in parkin-dependent mitophagy (Narendra et al., 2010). Finally, other E3 ubiquitin-ligases, such as NEDD4 and malin (officially known as DRG1 and NHLRC1, respectively) also promote SQSTM1 ubiquitylation (Lin et al., 2017; Sánchez-Martín et al., 2015). Although these modifications do not result in the degradation of SQSTM1, their possible implications for the regulation of autophagy remain to be addressed.

Assembling the cargo – shifting from mere aggregates to active condensates

An essential step for selective autophagy is the selection, concentration and separation of target materials by autophagy receptors, allowing them to be isolated by the autophagic machinery. It has previously been thought that SQSTM1 achieved this cargo clustering by forming aggregates (Bjørkøy et al., 2005; Komatsu et al., 2007) (Fig. 2A). However, two recent publications showed that the structures formed by SQSTM1 undergo phase-separation and have liquid-like properties that depend on the presence of ubiquitin chains (Sun et al., 2018; Zaffagnini et al., 2018) (Fig. 2B).

This finding constitutes a paradigm shift because the phase-separated droplets formed by SQSTM1 allow an exchange of their components, including ubiquitin and LC3, with the surrounding environment. In the aggregate model, by contrast, the cargo is presumed inactive and lacking mobility. Inside a liquid-like droplet, however, molecules are predicted to maintain their conformation and activity. Consequently, the droplets could also serve as nodes, from which signaling cascades are activated in the context of selective autophagy (Sun et al., 2018).

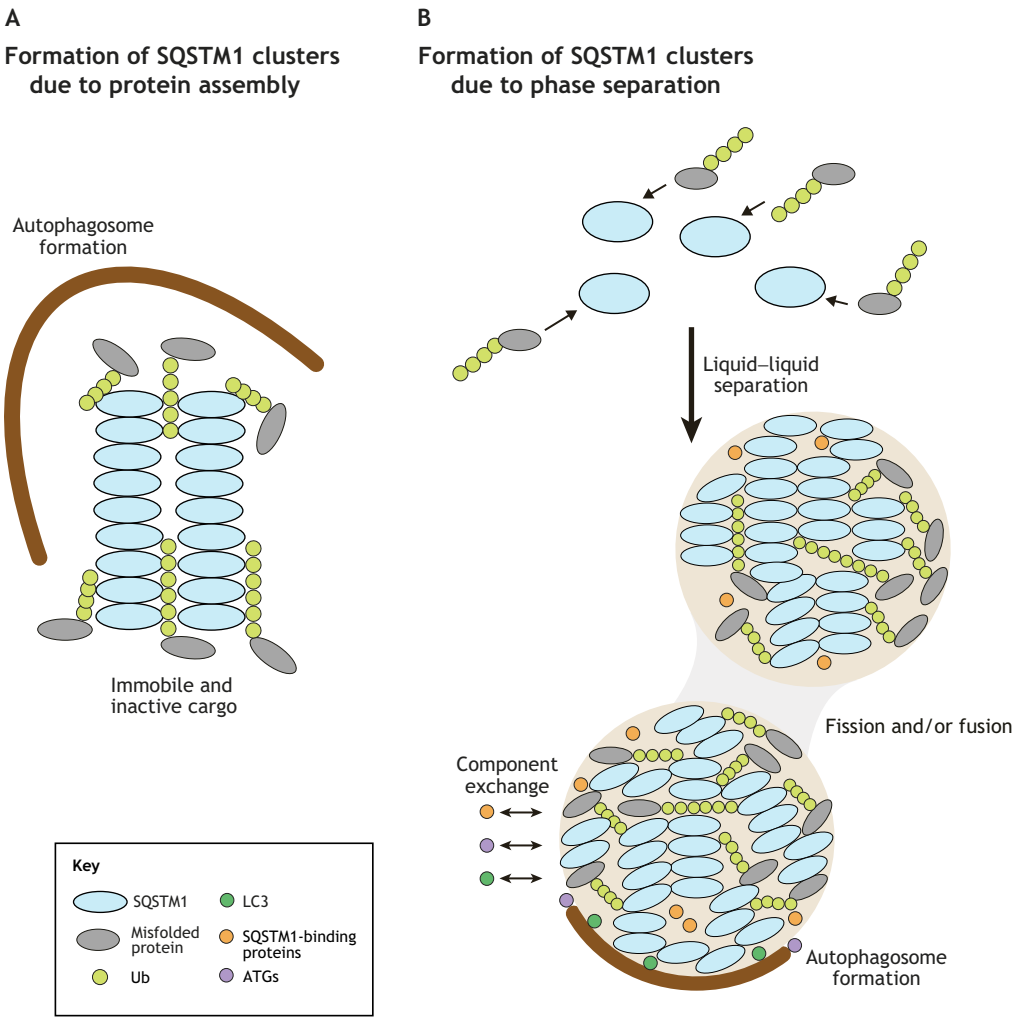

Fig. 2. Two mechanisms for the formation of SQSTM1 bodies during autophagy. (A) Previous model, in which SQSTM1 has been thought to form clusters through the aggregation of the cargo. (B) Current model, describing SQSTM1 cargo assembly on the basis of phase separation. In the presence of ubiquitin chains, SQSTM1 promotes the generation of biomolecular condensates formed by liquid-like phase separation. These liquid-like droplets allow the exchange of material with the surrounding medium and the formation of multimolecular complexes, and also undergo fusion and/or fission events with other phase-separated droplets. The autophagosomal membrane subsequently arises around these droplets to engulf the autophagic cargo. Ub, ubiquitin, ATGs, autophagy-related genes.

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The second study also supports the model of a liquid-like phase separation (Zaffagnini et al., 2018). SQSTM1 clustering appears to require multiple ubiquitin chains of at least three ubiquitin moieties. Various ubiquitin chain linkages, but especially K63, are able to promote clustering, whereas free monoubiquitin or unanchored ubiquitin chains, specifically the K48 linkage, inhibit SQSTM1 clustering (Zaffagnini et al., 2018). These SQSTM1 structures arise from existing SQSTM1 filaments that are crosslinked through polyubiquitylated substrates (Ciuffa et al., 2015; Zaffagnini et al., 2018). Inside these clustered droplets, SQSTM1 appears to retain little mobility, whereas ubiquitin, LC3 and other components may be able to diffuse more easily within the cluster and the surrounding cytosol (Sun et al., 2018; Zaffagnini et al., 2018). Finally, cluster formation is rendered more efficient by the presence of NBR1

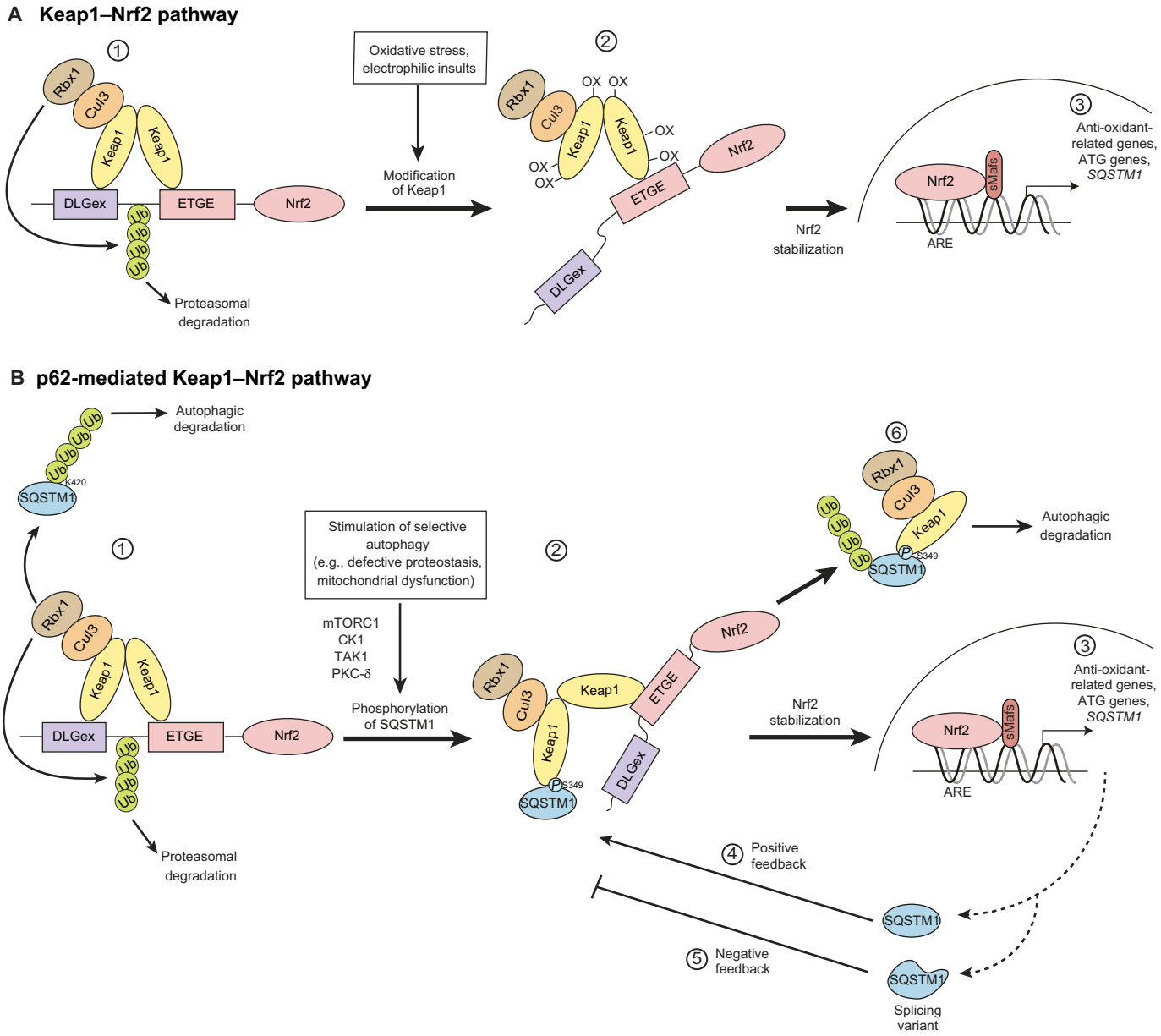

Fig. 3. The Keap1–Nrf2 pathway. (A) Overview of the canonical Keap1–Nrf2 pathway. (1) Keap1 is an adaptor protein for Cul3-based Rbx1 ubiquitin-ligase. The Keap1 homodimer recognizes a Nrf2 monomer through binding to two sites, a tight interaction with its ETGE motif and a weaker one with its DLGex motif, both of which are indispensable for sufficient ubiquitylation of Nrf2 by Rbx1. Consequently, Nrf2 is constantly ubiquitylated by the ubiquitin ligase and degraded by the proteasome. (2) Upon oxidative stress and/or exposure of electrophilic insults, certain cysteine residues of Keap1 are modified by reactive oxygen species and electrophiles (OX), which results in the dissociation of Nrf2 from Keap1. (3) Nrf2 is translocated to the nucleus to activate its target genes together with the transcription factors small Mafs (sMafs). (B) SQSTM1-mediated Keap1–Nrf2 pathway. (1) Under basal conditions, similar to the canonical pathway, the Keap1–Cul3–Rbx1 complex binds to and ubiquitylates Nrf2, which promotes its proteasomal degradation. The ubiquitin ligase also stimulates autophagic degradation of SQSTM1 through its ubiquitylation. (2) In response to stimuli of selective autophagy, such as defective proteostasis, mitochondrial dysfunction and invasive microbes, Ser349 of SQSTM1 is phosphorylated by mTORC1, CK1 (CSNK1A1), TAK1 and PKCδ, which abrogates the interaction between Keap1 and the DLGex motif of Nrf2, resulting in the prevention of binding of newly synthesized Nrf2 to Keap1. (3) Consequently, Nrf2 is stabilized and translocated to the nucleus to promote the expression of its target genes, which include *SQSTM1*. As a result, two SQSTM1 isoforms are upregulated: (4) a full-length form that promotes Nrf2 activation through a positive feedback loop, and (5) a splice variant that lacks the Keap1-interacting region (KIR) that negatively regulates the pathway. Ubiquitination of SQSTM1 on lysine 420 by the Keap1–Cul3–Rbx1 complex increases its autophagic degradation, whether it is in complex with Keap1 (6) or not (1). ARE, antioxidant response element.

(Zaffagnini et al., 2018), another autophagic receptor that cooperates with SQSTM1 in cells (Kirkin et al., 2009).

Tuning the switches – inner regulation of the SQSTM1–Keap1–Nrf2 axis by its core members

NF-E2-related factor 2 (Nrf2) is a master regulator of the oxidative stress response. Under basal conditions, Nrf2 is degraded by the 26S proteasome due to its interaction with its binding partner Kelch-like ECH-associated protein 1 (Keap1), which is an adaptor for the Cul3-based Rbx1 ubiquitin ligase complex (Fig. 3A, step 1). Under conditions of oxidative stress, oxidation of certain cysteine residues of Keap1 prevents Keap1-mediated proteasomal degradation of Nrf2. Nrf2 then translocates to the nucleus, where it induces the expression of genes that contain the antioxidant response element (ARE) in their regulatory regions (Fig. 3A, step 2). Nrf2 regulates the expression of >500 genes, including those encoding detoxifying enzymes, stress response proteins, metabolic enzymes, as well as autophagy-related (ATG) proteins and selective adaptors, such as NDP52, and SQSTM1 itself (Bellezza et al., 2018; Jain et al., 2010; Jo et al., 2014).

In 2010, a non-canonical mechanism of Nrf2 activation was discovered (Komatsu et al., 2010; Lau et al., 2010). The *SQSTM1* gene is a target of Nrf2, and the SQSTM1 protein interacts with Keap1, inhibiting the ability of Keap1–Cul3–Rbx1 ubiquitin ligase to promote Nrf2 degradation, thereby stabilizing and activating Nrf2 (Fig. 3B). Subsequent research has shed light on how this competitive interaction occurs. For Nrf2 to be efficiently ubiquitylated by the Keap1–Cul3–Rbx1 ubiquitin ligase, a Keap1 homodimer interacts through its double glycine repeat and C-terminal region (DC) domains with two motifs within Nrf2: a tight interaction with the Nrf2 ETGE motif and a weaker one with the DLGex motif, a sequence within the Neh2 domain of Nrf2 that contains both the classic DLG motif and the DIDLID element (Fig. 3B, step 1) (Fukutomi et al., 2014; Padmanabhan et al., 2006; Tong et al., 2007). The KIR domain of SQSTM1 also interacts with the DC domain of Keap1 in a manner that is similar to Nrf2; however, under basal conditions, the binding–dissociation constant between the DC domain of Keap1 and the KIR domain of SQSTM1 is lower than that of the Keap1 DC domain with the two motifs within Nrf2. Nevertheless, when SQSTM1 undergoes phosphorylation at serine 349 – as is the case under conditions that induce selective autophagy – its binding affinity for the Keap1 DC domain becomes higher than that for the Nrf2 DLGex motif (Fig. 3B, step 2). Consequently, phosphorylation of SQSTM1 disrupts one of the two interactions between Keap1 and Nrf2 that are required for Nrf2 ubiquitylation, thereby promoting Nrf2 activity (Fig. 3B, step 3) (Ichimura et al., 2013; Komatsu et al., 2010). Multiple kinases, including casein kinase 1 (CSNK1A1), transforming growth factor beta-activated kinase 1 (TAK1, officially known as MAP3K7), mTORC1 and PKC-delta (PRKCD), promote this phosphorylation during selective autophagy (Hashimoto et al., 2016; Ichimura et al., 2013; Jiang et al., 2017; Watanabe et al., 2017).

A physiological problem arises with this non-canonical mechanism, referred to as the SQSTM1-mediated Keap1–Nrf2 pathway, when autophagy is defective, as accumulation of SQSTM1 leads to persistent activation of Nrf2, which causes tissue damage and tumorigenesis in liver of hepatocyte-specific *Atg7*-knockout mice (Ichimura et al., 2013; Inami et al., 2011; Komatsu et al., 2007, 2005; Saito et al., 2016; Takamura et al., 2011). However, recent studies have revealed two mechanisms of how the SQSTM1-mediated Keap1–Nrf2 pathway is regulated by its own components.

As mentioned above, lysine 420 of the UBA domain of SQSTM1 is ubiquitylated by the Keap1–Cul3–Rbx1 complex (Lee et al., 2017). This ubiquitylation promotes sequestration of SQSTM1 and degradation of SQSTM1-clustered structures by autophagy (Lee et al., 2017), in line with a previous publication suggesting a role for Keap1 in promoting SQSTM1-mediated autophagic clearance (Fan et al., 2010). Although it is unclear whether Keap1 is degraded together with SQSTM1 under these conditions, this modification could have a double function. On one hand, weak, transient interactions of unphosphorylated SQSTM1 with Keap1 under basal conditions might lead to the ubiquitylation and subsequent degradation of SQSTM1, thus preventing SQSTM1-mediated release of Nrf2 (Fig. 3B, step 1). On the other hand, a tight interaction of Keap1 and SQSTM1 phosphorylated at serine 349 might facilitate SQSTM1 ubiquitylation, followed by its degradation together with that of Keap1, thereby liberating Nrf2 (Fig. 3B, step 6). In agreement with this idea is the observation that Keap1 is mainly degraded by autophagy (Taguchi et al., 2012), probably in a SQSTM1-dependent manner, as a recent report points out (Cloer et al., 2018). Additionally, the fact that both the PB1 and UBA domains of SQSTM1 are required for its ubiquitylation indicates that Keap1 can regulate SQSTM1 activation by switching its state from inactive dimers that are bound by the UBA domain to active oligomers linked through its PB1 domain. A similar control of the oligomeric state of SQSTM1 could be mediated by SQSTM1-activating ubiquitylation on the same lysine by UBE2D2 or UBE2D3 during ubiquitylation stress (Peng et al., 2017), whereas ubiquitylation of SQSTM1 on lysine 7 by TRIM21 impairs SQSTM1 oligomerization and prevents Keap1 sequestration (Pan et al., 2016).

We have recently proposed another mechanism for the regulation of the SQSTM1–Keap1–Nrf2 axis (Kageyama et al., 2018). We identified a splicing variant of SQSTM1 that is under the control of Nrf2 and functionally active as an autophagic receptor but, unlike the full-length form, lacks the region responsible for the interaction with Keap1. Lack of this region renders it unable to competitively inhibit the Keap1–Nrf2 interaction or promote autophagic degradation of Keap1. Therefore, this SQSTM1 variant, which is also induced during oxidative stress, promotes the association of Keap1 with Nrf2 and, thus, proteasomal degradation of Nrf2. This mechanism could allow the cell to avoid a deleterious persistent activation of Nrf2, counteracting the positive-feedback loop executed by full-length SQSTM1 (Fig. 3B, step 5).

Cycling and trafficking – other PTM-regulated functions of SQSTM1

Another recently described role of SQSTM1 is in the regulation of the endocytic pathway. Non-degradative ubiquitylation of SQSTM1 by the E3 ligase RNF26 at an undefined lysine residue promotes the recruitment of endocytic vesicles to the perinuclear region (Jongsma et al., 2016). This modification, which can be reversed by the deubiquitinating enzyme USP15, allows the formation of a perinuclear vesicle ‘cloud’, from which only selected vesicles are then released to undergo fast bidirectional transport to the cell periphery (Jongsma et al., 2016). This observation is in agreement with a previous report showing that SQSTM1 is required for normal dynein function and trafficking (Calderilla-Barbosa et al., 2014), and the initial observation on the participation of SQSTM1 in endosomal trafficking (Sanchez et al., 1998).

In addition, SQSTM1 phosphorylation at threonine 269 and serine 272 during early mitosis allows the cell to properly enter and exit this phase of the cell cycle. This modification is catalyzed by cyclin-dependent kinase 1 (CDK1) and is required to maintain appropriate levels of cyclin B1 and CDK1 through a yet undefined mechanism, thereby promoting timely progression of the cell cycle and avoiding tumorigenesis (Linares et al., 2011).

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SQSTM1 at the gates of Janus – marking the boundaries between health and diseases

Given the position of SQSTM1 at the crossroads of so many cellular pathways, it is not surprising that disruption of SQSTM1 homeostasis is linked to multiple human diseases. Further, to date, a large number of missense mutations of SQSTM1 have been identified in Paget's disease of bone (PDB), amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) (Rea et al., 2014). Though not all *SQSTM1* mutations have yet been verified, these mutations are accompanied by abnormalities in NF-κB signaling, SQSTM1-mediated autophagy and Nrf2 activation. In this section, we discuss how SQSTM1 interacts with pathological processes and how impairment of SQSTM1 function by accumulation, loss or mutation promotes various pathologies (Fig. 4).

Cancer

One of the first works to evaluate to role of SQSTM1 in cancer showed that SQSTM1 accumulation is linked to upregulation of NF-κB (Durán et al., 2008), a pro-survival pathway with which SQSTM1 had already been associated (Sanz et al., 2000, 1999). NF-κB controls gene expression of *SQSTM1* and can establish a positive feedback loop that is required for Ras-induced tumor progression (Durán et al., 2008; Ling et al., 2012).

The rapid growth of cancer cells also benefits from the anabolic pathways that are upregulated by mTORC1 (Saxton and Sabatini, 2017). SQSTM1 had been implicated in mTORC1 activation in response to an abundance of amino acids (Durán et al., 2011; Linares et al., 2015, 2013). In this context, accumulation of SQSTM1, which is tumorigenic itself (Umemura et al., 2016), facilitates the growth of tumor cells through the access to basic building blocks provided by hyperactivation of mTORC1 (Linares et al., 2015; Umemura et al., 2016).

Early work with hepatocyte-specific *Atg7*-knockout mice revealed liver injury and subsequent liver tumorigenesis accompanied by the accumulation of ubiquitin-positive structures (Komatsu et al., 2005). Subsequently, these observations were complemented by the discovery that Keap1 as well as S349-phosphorylated SQSTM1 are present on these structures, suggesting that loss of autophagy is coupled with persistent activation of Nrf2 (Ichimura et al., 2013; Saito et al., 2016). The deleterious phenotypes observed were markedly suppressed by the additional loss of *Sqstm1* or *Nrf2*, implying that the primary cause of tissue damage and tumorigenesis is the constant activation of Nrf2 in a SQSTM1-dependent manner (Komatsu et al., 2007; Ni et al., 2014).

In addition, accumulation of SQSTM1-positive structures called Mallory–Denk bodies is frequently observed in liver cells of patients

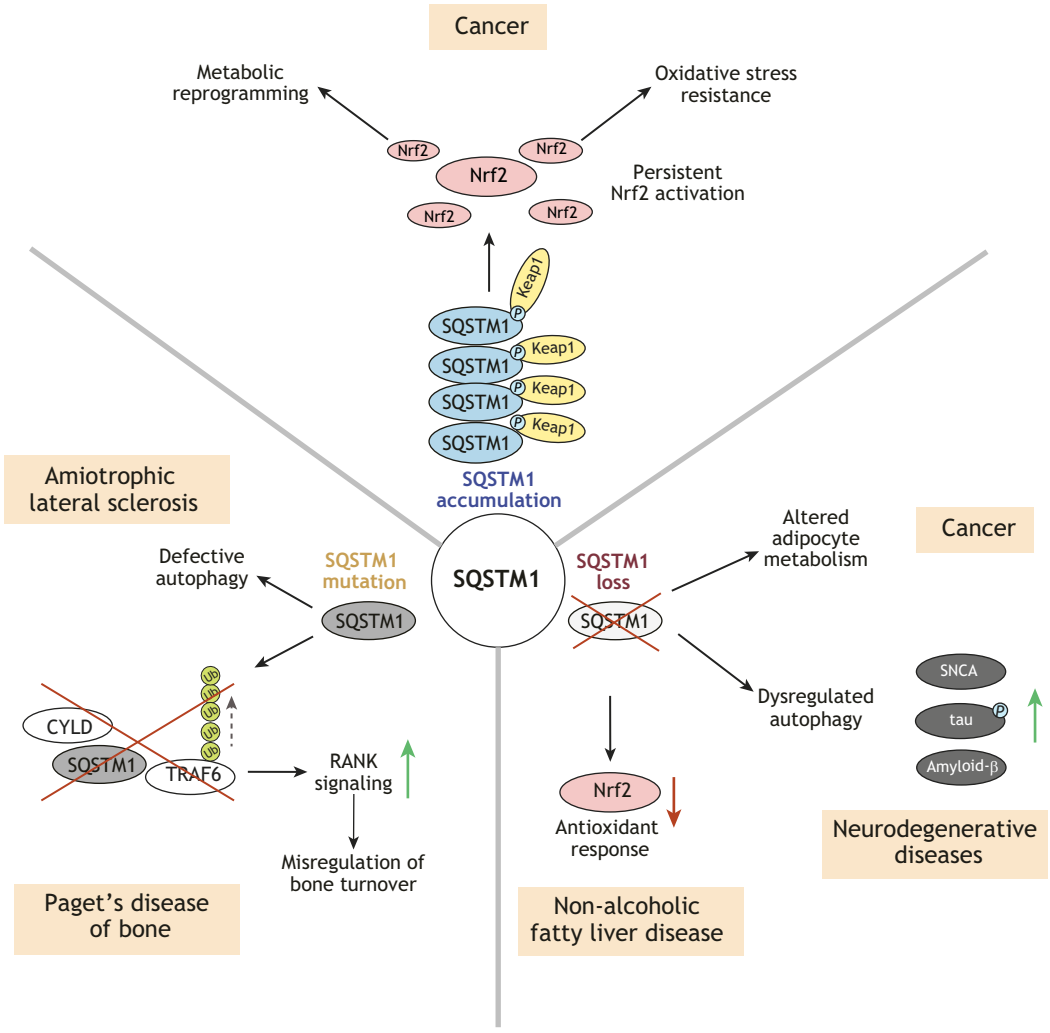

Fig. 4. Disease-related alterations of SQSTM1. As outlined here, the homeostatic functions of SQSTM1 can be impaired by its accumulation or loss or mutation, resulting in several pathological conditions. See main text for further details.

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diagnosed with liver disorders, including hepatocellular carcinoma (HCC) (Stumptner et al., 2002; Zatloukal et al., 2002). These bodies, which can be promoted by loss-of-function of DEPDC5 (an mTOR regulator the loss of which results in autophagy impairment) (Mizuno et al., 2018), contain high levels of S349-phosphorylated SQSTM1 and are associated with Nrf2 activation (Ichimura et al., 2013; Saito et al., 2016; Shimizu et al., 2016). Besides inducing resistance to oxidative stress, SQSTM1 and Nrf2 induce resistance of HCC cells against anti-cancer therapies that promote ferroptosis, a regulated form of cell death caused by iron-mediated accumulation of lipid peroxides (Sun et al., 2016). Furthermore, Nrf2 promotes cancer progression through metabolic reprogramming, including a switch in glucose metabolism towards nucleotide production that is required for proliferation (DeNicola et al., 2015; Mitsuishi et al., 2012). Accordingly, in HCC, the SQSTM1–Keap1–Nrf2 axis promotes metabolic reprogramming that includes enhanced production of uridine diphosphate (UDP)-glucuronate and glutathione, both of which promote cancer development as well as its resistance to anti-cancer drugs (Saito et al., 2016; Umemura et al., 2016). This prominent role of the SQSTM1–Keap1–Nrf2 axis in tumorigenesis has been extended to other cancer forms, including ovarian (Xia et al., 2014), pancreatic (Todoric et al., 2017), breast (Ryoo et al., 2018; Xu et al., 2017), lung (Huang et al., 2016) and arsenic-induced skin cancers (Shah et al., 2017), as well as multiple myeloma (Riz et al., 2016) and esophageal squamous cell carcinoma (Shi et al., 2018). In the case of pancreatic ductal adenocarcinoma (PDAC), SQSTM1-mediated activation of Nrf2 also results in the induction of the ubiquitin ligase MDM2, which further aggravates cancer progression by promoting degradation of p53 and inducing the Notch signaling pathway (Todoric et al., 2017). This Nrf2-dependent MDM2 activation may also be present in cells persistently infected with hepatitis C virus, where it results in degradation of retinoblastoma-associated protein (RB1) and development of HCC (Aydin et al., 2017). Besides, there are at least two other main signaling pathways affecting cancer development through SQSTM1, namely NF-κB and mTORC1 (Reina-Campos et al., 2018).

In contrast to these deleterious effects of SQSTM1 accumulation, claudin 1, a protein upregulated in multiple forms of cancer, induces SQSTM1 degradation through enhanced autophagy (Kim et al., 2018). Furthermore, loss of SQSTM1 in adipocytes promotes tumorigenesis by increasing the availability of nutrients to cancer cells (Huang et al., 2018a), and loss of SQSTM1 in hepatic stellate cells potentiates HCC progression through impairment of vitamin D receptor-mediated inhibition of inflammation and fibrosis (Durán et al., 2016), whereas double-knockout of SQSTM1 and Nrf2 in mice results in non-alcoholic steatohepatitis and liver tumors (Akiyama et al., 2018). Loss of SQSTM1 in stromal fibroblasts of prostate cancer cells induces an altered phenotype that establishes a pro-tumorigenic inflammatory environment by the secretion of pro-survival cytokine interleukin 6 (IL-6) (Valencia et al., 2014), establishing that SQSTM1 has a key role in the interplay of the different compartments of the tumor microenvironment: while tumor cells benefit from increased levels of SQSTM1 through the mechanisms described above, they also benefit from loss of SQSTM1 in stromal cells surrounding the tumor, as this results in metabolic changes that provide cancer cells with increased levels of nutrients and pro-survival signals (Reina-Campos et al., 2018).

Metabolic diseases

Dysregulation of SQSTM1 is also involved in multiple metabolic diseases (Long et al., 2017). SQSTM1 controls adipogenesis and body weight through regulation of ERK1 signaling (Lee et al., 2010; Rodriguez et al., 2006) and modulation of leptin signaling (Harada et al., 2013), respectively. Indeed, in mice, loss of *Sqstm1* causes insulin resistance and impaired glucose tolerance due to hyper-activation of ERK1 signaling (Rodriguez et al., 2006). *Sqstm1*-knockout mice exhibit hyperphagia owing to leptin resistance in the brain (Harada et al., 2013). SQSTM1 is also involved in inflammation of adipose tissue (Kratz et al., 2014). The reduced levels of SQSTM1 in visceral adipose tissue of obese people might explain why these processes are altered in this condition (Kosacka et al., 2015), as loss of SQSTM1 in adipose tissue in mice results in obesity due to impaired mitochondrial function (Müller et al., 2013). In addition, SQSTM1 plays a key role in non-alcoholic fatty liver disease, as it prevents ROS-derived apoptosis by inducing the Nrf2-mediated antioxidant response (Lee et al., 2016a; Park et al., 2015). Its loss, by contrast, facilitates the progression to HCC (Durán et al., 2016). Additionally, SQSTM1 induces apoptosis of macrophages in response to acute exposure to monosodium urate crystals, which is linked to the acute inflammatory response during the early phase of gout (Kim et al., 2016). Finally, the ability of SQSTM1 to sequester cytotoxic ubiquitylated proteins has been proposed to protect against atherosclerosis (Sergin et al., 2016).

Skeletal and muscular disorders

Mutations in SQSTM1 are strongly associated with PDB (Laurin et al., 2002), a chronic and progressive skeletal disorder characterized by focal areas of increased and disorganized bone turnover (Numan et al., 2015). These mutations mainly localize to the UBA domain of SQSTM1 and are causative in ∼50% of the cases of familial PDB (Goode et al., 2014; Rea et al., 2014). Although additional research is required to clarify the exact molecular mechanism, SQSTM1 can regulate osteoclast activity through the recruitment of the deubiquitinating enzyme CYLD to the RANK–TRAF6 complex (Jin et al., 2008). This promotes NF-κB activation through ubiquitylation of downstream effectors and this recruitment is dependent on the UBA domain of SQSTM1 (Jin et al., 2008). These observations are in agreement with a previous report on the relevance of SQSTM1 in RANK–TRAF6 signaling in bone remodeling (Durán et al., 2004). UBA-domain mutants of SQSTM1, which are causative of the disease, are unable to perform this function; consequently, CYLD cannot deubiquitylate TRAF6, resulting in enhanced RANK signaling and non-physiological osteoclast activation, one of the primary causes of familial PDB (Jin et al., 2008; Ralston and Layfield, 2012). Interestingly, an SQSTM1 mutation previously associated with PDB has also been detected in patients with rimmed vacuolar myopathy, but it remains unclear how the same mutations in SQSTM1 lead to such disparate phenotypes (Bucelli et al., 2015). Infection with the measles virus is an environmental factor that may contribute to PDB (Numan et al., 2015). The measles virus has a curious relationship with autophagy: it both uses autophagy to improve its infectious potential and is degraded during the process (Rozières et al., 2017). Unlike other components of the autophagic machinery, SQSTM1 mainly promotes an anti-viral response during infection (Petkova et al., 2017). Thus, PDB-associated mutations of SQSTM1 might impair its protective role against measles infection, thereby promoting the disease. This observation is supported by the severity of the phenotypes resulting from SQSTM1 mutation in combination with measles infection, compared to the effect of each of these individually (Kurihara et al., 2011).

Neurodegenerative diseases

Similar to Mallory–Denk bodies in the liver, phosphorylated SQSTM1 accumulates and colocalizes with inclusion bodies in

several neurodegenerative diseases. Additionally, SQSTM1 is one of the first markers, together with ubiquitin, to appear in tau (officially known as MAPT) and SNCA inclusions (Kurosawa et al., 2016; Kuusisto et al., 2001). Together with the membrane-damage sensor galectin-8 and the autophagy adaptor NDP52, SQSTM1 promotes the autophagic degradation of seeded tau under normal conditions, thereby preventing its propagation throughout the brain (Falcon et al., 2018). In agreement with this observation, loss of SQSTM1 has been associated with neurodegeneration and accumulation of hyperphosphorylated tau (Ramesh Babu et al., 2008). Expression levels of SQSTM1 are decreased in several neurodegenerative diseases owing to age-related DNA oxidative damage (Du et al., 2009a,b). Accordingly, induction of *Sqstm1* through gene therapy has been shown to decrease the levels of amyloid beta precursor protein through an activation of autophagy and to rescue cognitive deficits in mice models of Alzheimer's disease (Caccamo et al., 2017).

Amyotrophic lateral sclerosis

Some of the PDB-associated SQSTM1 mutations are shared with amyotrophic lateral sclerosis (ALS), an age-dependent neurodegenerative disease of motor neurons that is linked to a decline in mechanisms controlling protein quality (Rea et al., 2014). In addition, SQSTM1-positive inclusions have been detected in C9ALS, the most common form of ALS (King et al., 2013; Troakes et al., 2012). It is thought that the SQSTM1 mutations that are common in PDB and ALS cause deficits in the autophagic machinery, thereby decreasing the ability of the cell to maintain proteostasis (Nguyen et al., 2018; Rea et al., 2014). Similarly, an ALS-associated mutation of SQSTM1 has been identified in its LIR domain, further pointing to defective autophagy as a causative mechanism of the disease (Goode et al., 2016). Autophagy is also impaired by ALS-associated mutations in TBK1, a kinase responsible for phosphorylation of SQSTM1 at serine 403 (Oakes et al., 2017). However, the role of autophagy in ALS remains elusive (Nguyen et al., 2018), as some reports suggest that – in ALS cases caused by mutations of superoxide dismutase 1 (SOD1) – autophagy is neuroprotective at early stages of the disease but deleterious in the advanced stages (Rudnick et al., 2017; Zhang et al., 2013). This parallels the dual role of aggregated mutant SOD1 (mSOD1) in autophagy, as it upregulates autophagy initiation, while impairing axonal transport of the autophagosome and its fusion with the lysosome. However, how mSOD1 causes these alterations remains poorly understood (Nguyen et al., 2018). SQSTM1 may play an additional role in this disease, as it is able to interact with mutant forms of SOD1, independently of its UBA domain, to sequester and protect it from degradation, thereby aggravating the pathological outcome (Gal et al., 2007, 2009; Hadano et al., 2016). In spinal muscular atrophy, another motor neuron disease, SQSTM1 is also arising as a new therapeutic target. This is because loss of survival motor neuron protein 1 (SMN1) – that triggers the disease – is counteracted in fly and mouse models through downregulation of SQSTM1, which increases SMN1 levels and, in turn, results in better disease survival (Rodriguez-Muela et al., 2018).

Huntington's disease

An interesting role for SQSTM1 is apparent in Huntington's disease, a neurodegenerative disorder caused by trinucleotide repeat expansion in the Huntingtin gene (*Htt*) (Pagan et al., 2017). Normal HTT serves as a scaffold protein during selective autophagy (Rui et al., 2015) where it associates with SQSTM1. This facilitates interaction of SQSTM1 with LC3 and ubiquitylated substrates. Additionally, HTT releases ULK1 kinase from negative regulation through mTOR, a step required for initiation of autophagy (Rui et al., 2015). This is consistent with previous observations that ULK1 promotes the phosphorylation of serine 407 in SQSTM1 to alleviate proteotoxic stress (Lim et al., 2015).

However, trinucleotide repeat amplification in *Htt* produces a polyglutamine expansion, resulting in a mutant form of HTT (mHTT) that is aggregate-prone and must be removed from the cell. Unlike other neurodegenerative diseases that present with reduced autophagic flux (Menzies et al., 2011), mouse models and human lymphoblasts of Huntington's disease patients display normal autophagic flux with increased numbers of autophagosomes that, however, do not contain cargo proteins, probably due to a defective cargo recognition (Martin et al., 2015). It is tempting to speculate that autophagy malfunction in this disease is caused by dysregulation of normal HTT functions, leading to enhanced initiation of autophagy with defective SQSTM1 function.

Autophagy-mediated degradation of this type of aggregation-prone protein is orchestrated by SQSTM1, together with the co-caperone BAG3 that is involved in chaperone-assisted autophagy, and chaperones HSP70 and HSPB8 (Stürner and Behl, 2017) that are induced by activation of AMPK (Walter et al., 2016), and kept active during aging by Nrf2 (Tang et al., 2018). IRE1 and ENC1 are components of the ER stress response that downregulate autophagic flux by interfering with SQSTM1 function, thereby impairing the degradation of protein aggregates with subsequent deleterious effects (Lee et al., 2016b, 2012). By contrast, cereblon (CRBN), a subunit of the Cul4 ubiquitin ligase complex, appears to downregulate SQSTM1-mediated aggregate formation in primary cortical neurons, resulting in a cytoprotective effect (Zhou et al., 2018). Bcl-2 also decreases the ability of SQSTM1 to bind and cluster ubiquitylated cargos, but the effect of this downregulation during neurodegeneration has not yet been assessed (Zhou et al., 2015). Interestingly, when still in a soluble form, mHTT can adopt multiple conformations, some of which are less ubiquitylated and, thus, less efficiently recognized by SQSTM1. This results in a decreased degradation and increased toxicity of the protein (Sun et al., 2017). Likewise, a recent publication has shown that the degree of polyglutamine expansion of HTT influences the localization and target recognition of SQSTM1, thereby affecting the vulnerability to proteotoxic stress (Huang et al., 2018b).

Parkinson's disease

Multiple lines of evidence also link SQSTM1 with the pathophysiology of Parkinson's disease (PD). Loss of SQSTM1 results in increased accumulation and phosphorylation of α-synuclein (SNCA), a molecular hallmark of the disease (Tanji et al., 2015). Mutations in *LRRK2* are responsible for the most common monogenic form of PD, as mutant LRRK2 dysregulates the formation of protein aggregates and their autophagic degradation during the disease (Bang et al., 2016; Bravo-San Pedro et al., 2012). Moreover, recent findings indicate that LRRK2 interacts with SQSTM1 and directly regulates multiple phosphorylation events on SQSTM1, further emphasizing the pathogenic effects of mutant LRRK2 (Kalogeropulou et al., 2018).

A secondary but crucial function is performed by SQSTM1 during PINK1 and/or parkin (PRKN)-mediated mitophagy, a key process affected during PD. Upon mitochondrial damage, parkin is recruited to mitochondria to promote the isolation and degradation of the injured sections (Pickles et al., 2018). The role of SQSTM1 in this process is still under debate, as some authors claim it to be indispensable for parkin-mediated mitophagy (Geisler et al., 2010),

whereas others proposed that it is only required for mitochondrial clustering (Narendra et al., 2010; Okatsu et al., 2010). More recent findings suggest that this clustering is crucial for protecting cells against apoptosis, as it reduces the proteasomal degradation of outer mitochondrial membrane proteins, thereby preventing the release of the pro-apoptotic protein cytochrome c (Xiao et al., 2017). However, parkin appears to promote the proteasomal degradation of SQSTM1 because loss-of-function of parkin, either by mutation or oxidative stress, results in accumulation of SQSTM1 in neurons of the substantia nigra and striatum areas (Song et al., 2016).

On the basis of these findings, we suggest to divide the relationship between SQSTM1 and parkin into two different scenarios. Under basal conditions, parkin prevents accumulation of SQSTM1 through its proteasomal turnover; whereas, during mitophagy, parkin is redirected to mitochondrial targets and the resulting elevated levels of SQSTM1 can contribute to autophagic removal of the damaged organelle. Additionally, the level of SQSTM1 increases following inactivation of parkin because of oxidative stress, which may help the cell to cope with stress through induction of the anti-stress Nrf2 pathway, which is mediated by SQSTM1 (Komatsu et al., 2010; LaVoie et al., 2007). In agreement with this hypothesis, *SQSTM1* expression is upregulated during mitophagy through the nuclear translocation of transcription factors TFEB and Nrf2 (Ivankovic et al., 2016); and dysregulation of TFEB has been implicated in the pathogenesis of this type of neurodegenerative disease (Cortes and La Spada, 2018). This response might improve the ability of the cell to deal with threats by enhancing the antioxidant and clearance systems. However, it remains to be determined how these different aspects of the parkin–SQSTM1 axis intersect mechanistically, as a new study just reported that SQSTM1 also participates in parkin-independent mitophagy by promoting mitochondrial ubiquitylation through the recruitment of the Keap1-associated E3 ubiquitin ligase complex (Yamada et al., 2018).

Concluding remarks

As its functional network becomes more densely populated, interest in SQSTM1 grows. Currently, the protein is a diagnostic and prognostic marker in multiple forms of cancer, i.e. osteosarcoma, oral squamous cell carcinoma, cutaneous malignant melanoma, esophageal adenocarcinoma, ovarian, colon, breast and non-small cell lung cancers, and solid tumors (Adams et al., 2016; Daniels et al., 2013; Ellis et al., 2014; Giatromanolaki et al., 2014; Inoue et al., 2012; Iwadate et al., 2014; Liu et al., 2014a; Luo et al., 2013; Ma et al., 2018; Niklaus et al., 2017; Park et al., 2013; Ruan et al., 2018; Schläfli et al., 2016), and has attracted attention as a potential therapeutic target (Yan et al., 2017; Zhang et al., 2016). An antitumor SQSTM1 DNA vaccine has already been developed and trialed in humans (Gabai et al., 2014; Ponomarenko et al., 2017; Sabbieti et al., 2015; Venanzi et al., 2013); however, SQSTM1 can have both beneficial and deleterious effects depending on the pathological context, as is the case for autophagy itself (Dikic and Elazar, 2018). Then, any hope to develop successful therapeutic strategies in pathologies with SQSTM1 alterations needs to keep in mind the complexity of the SQSTM1 signaling network and how it is affected in each particular disease situation: its tight post-translational regulation, its role in autophagy, its function in the Keap1–Nrf2 axis and its role as a signaling hub.

Competing interests

The authors declare no competing or financial interests.

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