

## REVIEW

## SUBJECT COLLECTION: AUTOPHAGY

# Emerging roles of mitotic autophagy

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## ABSTRACT

Lysosomes exert pleiotropic functions to maintain cellular homeostasis and degrade autophagy cargo. Despite the great advances that have boosted our understanding of autophagy and lysosomes in both physiology and pathology, their function in mitosis is still controversial. During mitosis, most organelles are reshaped or repurposed to allow the correct distribution of chromosomes. Mitotic entry is accompanied by a reduction in sites of autophagy initiation, supporting the idea of an inhibition of autophagy to protect the genetic material against harmful degradation. However, there is accumulating evidence revealing the requirement of selective autophagy and functional lysosomes for a faithful chromosome segregation. Degradation is the most-studied lysosomal activity, but recently described alternative functions that operate in mitosis highlight the lysosomes as guardians of mitotic progression. Because the involvement of autophagy in mitosis remains controversial, it is important to consider the specific contribution of signalling cascades, the functions of autophagic proteins and the multiple roles of lysosomes, as three entangled, but independent, factors controlling genomic stability. In this Review, we discuss the latest advances in this area and highlight the therapeutic potential of targeting autophagy for drug development.

**KEY WORDS:** Autophagy, Chromosomal instability, Lysosomes, Mitosis, Chromosome segregation, Cancer

## INTRODUCTION

Mitosis is the shortest phase of the cell cycle, and during mitosis most biological processes are either shutdown or repurposed to support the correct distribution of the genetic material into the daughter cells. It is well accepted that dramatic morphological changes occur in mitotic cells, together with a massive reorganization of the cytoskeleton to support cell rounding, mitotic spindle formation and accurate mitotic exit (Pines, 2006). As cells enter mitosis, the actomyosin cortex is reshaped to support cell rounding, which is tightly coordinated with the microtubule network to establish spindle orientation and positioning (Kelkar et al., 2020; Lancaster and Baum, 2014; Petry, 2016). In cells undergoing open mitosis, the nuclear envelope (NE) breaks down at mitotic entry, a process primarily regulated by cyclin-dependent kinase 1 (CDK1)-cyclin B complexes (Alvarez-Fernández and Malumbres, 2014). NE breakdown results in the mixture of two compartments and the assimilation of the NE into the fragmented endoplasmic reticulum (ER) (Anderson and Hetzer, 2008).

Interestingly, mitotic degradation of NE components has not been demonstrated, whereas autophagy-dependent degradation of the nuclear lamina constituent lamin B1 has been characterized in interphase upon oncogenic stress (Dou et al., 2015). In parallel, cells face a drastic remodelling of organelles at mitotic onset (Champion et al., 2017), including the fragmentation of mitochondria (Pangou and Sumara, 2021), disruption of the ER (Kumar et al., 2019) and disassembly of the Golgi (Kano et al., 2000; Lowe et al., 2000; Colanzi et al., 2000). The unidirectionality of mitotic progression is ensured by the regulated proteolysis of mitotic factors driven by the ubiquitin-proteasome system (UPS) (Glotzer et al., 1991). However, to what extent the restructuring and redistribution of organelles intervene in the regulation of mitotic progression is not fully understood. Emerging evidence points to the lysosomes as novel regulators of mitotic progression, thus opening a largely unexplored field of research for further investigation.

The lysosome is the main degradative organelle in mammalian cells, and functions as a nutrient sensor and signalling hub (Ballabio and Bonifacino, 2020). The acidic milieu and enzymatic content of lysosomes enable the digestion of all types of biological material of different origins such as those obtained through biosynthetic, endocytic and autophagic pathways (Cullen and Steinberg, 2018; Yim and Mizushima, 2020). Three types of autophagy have been described so far: macroautophagy, chaperone-mediated autophagy (CMA) and microautophagy. Microautophagy refers to the direct engulfment of cytosolic substrates into the lysosomal lumen, whereas CMA-targeted proteins are recognized by the lysosome-associated membrane glycoprotein 2A (LAMP2A, an isoform of LAMP2) for their degradation (Massey et al., 2006). During macroautophagy (hereafter autophagy), autophagic vesicles named autophagosomes surround the cytosolic cargoes, before they fuse with lysosomes and form autolysosomes, in which degradation takes place (Klionsky et al., 2021a,b). The core molecular machinery controlling autophagy is well-understood and involves the sequential action of autophagy-related genes (ATGs) and accessory proteins to drive the membrane remodelling required for cargo engulfment and degradation. Briefly, the activation of the Unc-51-like autophagy-activating kinase 1/2 (ULK1/2) complex [containing ATG101, ATG13, RB1 inducible coiled-coil 1/FAK family kinase-interacting protein of 200 kDa (FIP200; also known as RB1CC1) and the Ser/Thr kinases ULK1 or ULK2] recruits the phosphatidylinositol 3-kinase catalytic subunit type 3 (PI3KC3) complex 1, formed by vacuolar protein sorting 34 (VPS34; also known as PI3KC3), vacuolar protein sorting 15 (VPS15, also known as p150 and PIK3R4), Beclin-1 and ATG14 (Wirth et al., 2013). The synthesis of phosphatidylinositol-3-phosphate (PI3P) at concrete sites in the ER leads to the recruitment of other ATG proteins and PI3P effectors, resulting in the nucleation and expansion of the phagophore. Selective recognition of substrates by autophagic receptors is known as selective autophagy (Gatica et al., 2018) and is mediated by selective-autophagy receptors (SARs) (Johansen and Lamark, 2020; Kim et al., 2016). SARs contain short amino acid sequences, named LC3-interacting motif

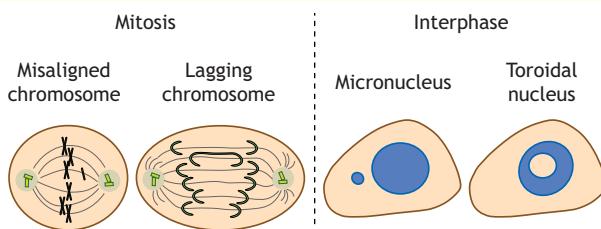
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**Box 1. Biomarkers of chromosomal instability**

Genomic stability is defined as the correct inheritance of genetic material throughout generations, and ultimately relies on the faithful distribution of chromosomes during mitosis. Perturbations of mitotic progression induced by defects in chromosome segregation or in surveillance pathways lead to the appearance of mitotic errors that underlie chromosomal instability (CIN) (Geigl et al., 2008). Chromosomal imbalance induced by CIN is a hallmark of cancer and contributes to intratumoral heterogeneity promoting anticancer drug resistance (Bakhour and Cantley, 2018; Hoevenaar et al., 2020; Hanahan and Weinberg, 2011). CIN is detectable in mitotic cells through a direct visualization of mitotic errors, such as misaligned chromosomes at metaphase and lagging chromosomes in cells exiting mitosis (see figure). Once cells re-enter interphase, CIN can be detected by the presence of atypical nuclear phenotypes, such as micronuclei or toroidal nuclei in the progeny (shown on the right) (Almacellas et al., 2021; Hämäläistö et al., 2020; Pons et al., 2022). Micronuclei form upon defects in chromosome segregation, which lead to the presence of a small portion of DNA surrounded by a NE in the cytosolic compartment (He et al., 2019; Krupina et al., 2021). A toroidal nucleus is characterized by a nucleus with a void containing cytosolic components, and its origin remains unclear (Almacellas et al., 2021; Naso et al., 2020; Verstraeten et al., 2011). Both phenotypes serve as biomarkers for CIN in interphase cells, which correspond to the majority of a cell population, and can be used to complement high-throughput screenings for genomic instability.



(LIR) or GABARAP-interacting motif (GIM), to promote their interaction with the ATG8 family members LC3A, LC3B and LC3C (also known as MAP1LC3A–MAP1LC3C), or GABARAP, GABARAPL1 and GABARAPL2, respectively (Johansen and Lamark, 2020; Rogov et al., 2017). The list of SARs continues to grow and highlights a central role of selective autophagy in biological processes, as well as in disease (Kirkin and Rogov, 2019; Johansen and Lamark, 2020). The first autophagic receptor identified was p62, also named sequestosome 1 (SQSTM1), which anchors ubiquitylated cargoes to lipidated ATG8 proteins (also denoted LC3-II). Interestingly, due to its ubiquitin-associated domain, p62 acts at the intersection between autophagy and the UPS (Moscat and Diaz-Meco, 2012; Fuchs et al., 2015; Hewitt et al., 2016). Although the function of SARs in mitosis is still understudied, recent findings highlight their potential role in mitotic progression, and future studies are needed to shed light onto their function in cell division.

The degradative function of lysosomes and canonical activation of autophagy have been largely studied in interphase cells, but our current understanding of the role of lysosomes in mitosis is still limited. Several studies show that the number of autophagic vesicles is reduced in mitotic cells compared to the number in interphase (Almacellas et al., 2021; Lu et al., 2019; Li et al., 2020; Hämäläistö et al., 2020; Odle et al., 2020), but they differ in the interpretation of the results. Although some authors propose an active shutdown of autophagy during cell division (Eskelin et al., 2002; Odle et al., 2020), others claim that even if autophagy were reduced, this process is important for a faithful chromosome segregation and preventing chromosomal instability (CIN) (Almacellas et al., 2021;

Liu et al., 2009; Li et al., 2020; Mathew et al., 2007). CIN is a well-defined hallmark of cancer (Hanahan and Weinberg, 2011) and mostly results from defective mitotic progression that can be scored by the analysis of CIN biomarkers in both mitotic and interphase cells (Box 1 and figure therein) (Pons et al., 2022). The importance of understanding the link between autophagy and/or lysosomes and CIN is supported by recent studies demonstrating that drugs targeting lysosome acidification promote the accumulation of mitotic errors, which might offer a therapeutic window in the context of cancer (Almacellas et al., 2021; Hämäläistö et al., 2020). There is also strong evidence for a causal association between autophagy deficiency and CIN based on genetic models (Joy et al., 2021; Delaney et al., 2020; Liu et al., 2016), but further characterization is needed to determine whether these effects are directly related to autophagy (Galluzzi and Green, 2019). Our ability to study organelle dynamics has stemmed from the rapid evolution of microscopy in the recent years, which offers new tools for cell biologists (Almacellas et al., 2022; Klionsky et al., 2021a,b). However, a better understanding of the mitotic function of autophagy and lysosomes will require the integration of the knowledge regarding signalling cascades, membrane trafficking and the recently described alternative functions of lysosomes, such as lysosomal leakage (Stahl-Meyer et al., 2021; Hämäläistö et al., 2020).

In this Review, we aim to discuss our current understanding of the upstream signals that regulate autophagy during mitotic progression. We highlight the novel paradigm of a requirement of lysosome-dependent degradation in cell division and examine additional functions of lysosomes and autophagic proteins beyond macroautophagy in mitosis.

### Signalling pathways regulating autophagy during mitotic progression

Inhibition of autophagy at the onset of mitosis has been initially proposed to protect the genetic material from degradation upon NE breakdown (Eskelin et al., 2002). However, growing evidence supports a positive role of autophagy and lysosomes during cell division to guarantee the faithful inheritance of genetic material. In this section, we will discuss the advances that have been made regarding the signalling pathways that control mitotic autophagy and outline some of the questions that remain to be addressed.

Two main kinases control autophagy induction, the energy sensor AMP-activated protein kinase (AMPK) and mammalian target of rapamycin complex 1 (mTORC1). Upon energy shortage, AMPK activates autophagy through direct phosphorylation of ULK1 on S317 and S777 to preserve energy homeostasis (Kim et al., 2011). Under nutrient-rich conditions, mTORC1, the prime regulator of cell growth, is active and inhibits autophagy by direct phosphorylation of ULK1 and/or ULK2 (ULK1/2) and ATG13 to support anabolic processes (Neufeld, 2010; Chang and Neufeld, 2009; Condon and Sabatini, 2019). Conversely, in response to nutrient deprivation or stress, mTORC1 is inhibited, thus releasing autophagy inhibition and consequently promoting autophagic flux.

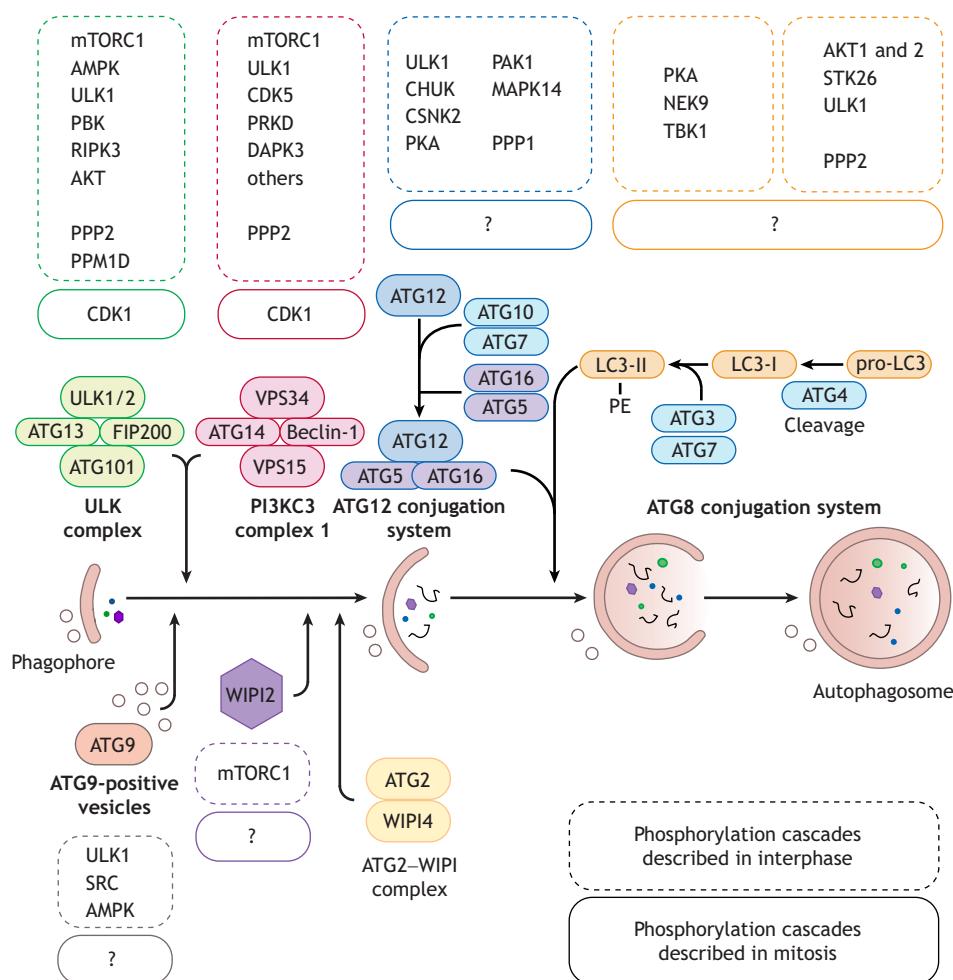
Over the past decades, phosphorylation has emerged as a main post-translational modification (PTM) involved in autophagy regulation, and the number of phosphorylation sites operating on ATG proteins and autophagy regulators keeps growing (reviewed in Licheva et al., 2021). Beyond the classical view of the mTORC1-AMPK axis as a master regulator controlling ULK1/2 activity, over 20 kinases and phosphatases have been identified in the regulation of interphase autophagy (Fig. 1) (Licheva et al., 2021). Interestingly, kinases such as CDK1 or AMPK have been proposed to regulate both

autophagy and mitosis (Li and Zhang, 2017). However, the interplay between these two cellular processes is still unclear and the number of kinases and phosphatases regulating mitotic autophagy is extremely low (Fig. 1). Specific approaches focusing on mitotic cells are needed to clarify whether the upstream signalling that controls autophagy differs between mitosis and interphase.

In recent years, several studies have explored the status of mTORC1 during mitosis. Despite divergent views regarding the control of autophagy initiation at mitotic entry, there is now a general agreement that mTORC1 is inhibited in mitotic cells (Moustafa-Kamal et al., 2020; Odle et al., 2020; Almacellas et al., 2021). It has been proposed that mTORC1 inhibition during mitosis is due to hyperphosphorylation of the regulatory-associated protein of mTOR (Raptor; also known as RPTOR) and the consequent displacement of mTORC1 from the lysosomal surface (Gwinn et al., 2008; Moustafa-Kamal et al., 2020; Odle et al., 2020). Conversely, other studies have reported the association of S2481-phosphorylated mTOR with the midbody during telophase, but its biological significance remains unresolved (Vazquez-Martin et al., 2012). In 2020, two elegant studies positioned CDK1 as a central regulator of mitotic autophagy and described CDK1-specific phosphorylation sites in ULK1 and ATG13, critical regulators of autophagy initiation (Li et al., 2020; Odle et al., 2020) (Fig. 1). However, these studies propose opposing roles of CDK1 in mitotic autophagy regulation. Whereas Odle et al. argue that CDK1-mediated phosphorylation of ULK1 inhibits autophagy initiation (Odle et al., 2020), Li et al. show

that autophagic flux persists in mitosis upon CDK1-dependent phosphorylation of ULK1 complex on multiple sites (Li et al., 2020). Indeed, phospho-inert alanine mutations in ULK1 and ATG13 do not cause alterations in their localization, or in ULK1 kinase activity, but concomitantly diminish autophagic flux as demonstrated by a reduction in p62 turnover and number of LC3 puncta in mitotic cells, as well as cause an increase of the ratio between GFP and mRFP in mutant cells expressing mRFP–GFP–LC3 tandem reporter (Li et al., 2020). Based on these studies, it appears that mitotic autophagy is insensitive to mTORC1 inhibition and that specific signalling pathways operate in dividing cells, which opens a new avenue for future research.

Another key event controlling autophagy initiation is the synthesis of PI3P at the initiation site, which induces the recruitment of WD repeat domain phosphoinositide-interacting protein (WIPI) proteins and triggers the formation and expansion of the phagophore. The lipid kinase PI3KC3 complexes orchestrate diverse cellular processes, including autophagy, endocytic sorting, phagocytosis, recruitment of retromer to endosomes, depending on its binding partners; complex 1 (see above for components) is involved in autophagy, whereas complex 2, which contains UV irradiation resistance-associated gene (UVRAG) instead of ATG14, also known as ATG14L and barkor, mainly controls the endocytic pathway (Jaber et al., 2016; Juhász et al., 2008; Ohashi et al., 2020; Bean et al., 2015). During mitosis, CDK1 inhibits VPS34 by phosphorylating T159, which impairs VPS34 binding to Beclin-1,



**Fig. 1. Overview of the kinases and phosphatases that control autophagy in interphase versus mitosis.** Autophagy is a multistep process that is strictly regulated by phosphorylation events controlling each stage. Several kinases and phosphatases have been characterized in interphase (highlighted with dotted outlines), but the number of kinases known to regulate mitotic autophagy is considerably lower (denoted with plain outlines). Until now, only CDK1 has been implicated in the regulation of mitotic autophagy by phosphorylating ATG13, ULK1 and VPS34. Whereas CDK1-mediated VPS34 phosphorylation has been proposed to be inhibitory, the functional consequences of the phosphorylation of ULK complex components are still under debate. AKT (green dashed box), AKT family proteins; ATG2, ATG2A and/or ATG2B; ATG9, ATG9A; CSNK2, casein kinase II; PE, phosphatidylethanolamine; PKA, protein kinase A; PPP2, protein phosphatase 2; PPP1, protein phosphatase 1; PRKD, PRKD1–PRKD3. WIPI4 is also known as WDR45.

thus reducing the synthesis of PI3P (Furuya et al., 2010). The authors propose an inhibition of autophagy through this phosphorylation, but how it affects other trafficking routes remains elusive. Interestingly, another study has reported that PI3P production by VPS34 at the midbody during mitotic exit favours the recruitment of zinc finger FYVE domain-containing protein 26 (FYVE-CENT; also known as spastizin or ZFYVE26), a centrosomal protein that is essential for the completion of cytokinesis (Sagona et al., 2010), suggesting that VPS34 function might be differentially regulated at different steps of mitotic progression. In addition, it has been described that WIPI2, an essential PI3P-binding effector promoting autophagy initiation, is degraded by the proteasome at the onset of mitosis (Lu et al., 2019).

The current discussion regarding the status of autophagy during mitosis focuses on whether this process is either activated or inhibited, whereas it is well-accepted that there is a gradient of autophagic activity in interphase. Upon entering mitosis, a cell undergoes intracellular remodelling that is accompanied by global changes in signalling cascades and morphological restructuring in a short period of time. In addition, the common readouts used for the study of autophagic flux have different dynamics, ranging from time scales of seconds for phosphorylation and dephosphorylation events to minutes for membrane remodelling and trafficking. These differences might explain the current discrepancies in the interpretation of the state of autophagy in mitotic cells. Owing to this complexity, study of autophagy in mitotic cells should be addressed differently than in interphase, as the signalling mechanisms driving autophagy initiation and its consequences on the autophagic flux in mitosis might be uniquely regulated.

#### Macroautophagy involvement for optimal cell division

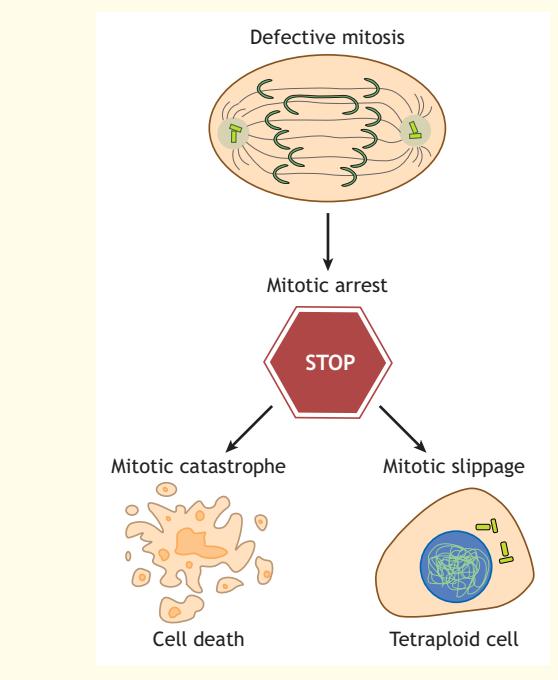
Targeted proteolysis of key mitotic proteins ensures the unidirectionality of mitotic progression and the correct segregation of genetic material. It is well established that the UPS is essential for the control of mitotic progression, as the anaphase-promoting complex/cyclosome (APC/C), a multiprotein E3 ligase, targets cell cycle proteins for proteasome-dependent degradation (Castro et al., 2005). Indeed, cells treated with inhibitors of the proteasome are halted in late G2 and are unable to enter mitosis (Almacellas et al., 2021; Rastogi and Mishra, 2012), supporting a fundamental role of UPS for entering mitosis. However, during mitosis, organelles and non-protein cellular components need to be degraded to guarantee the spatiotemporal control of mitotic progression. Alterations in lysosome trafficking or acidification induce a delay of mitotic progression and increase the prevalence of mitotic errors, supporting a role for lysosomes as active organelles that preserve mitotic fidelity (Almacellas et al., 2021; Hämäläistö et al., 2020). Accordingly, autophagy and lysosome-dependent degradation have been shown to play critical roles in cell survival during prolonged mitotic arrest (Box 2), although the role of autophagy in cell division remains controversial (reviewed in Mathiassen et al., 2017; Hämäläistö et al., 2021). In this section, we discuss the contribution of autophagy/lysosome-dependent degradation in the context of mitosis.

#### The cohesin complex

Chromosome segregation is controlled by the coordinated disassembly of the cohesin complex during the metaphase to anaphase transition. Deletion of cohesin components or associated proteins has been linked to CIN. For example, gain- and loss-of-function of wings apart-like protein homolog (WAPL), a regulatory protein involved in the detachment of the cohesin complex from

#### Box 2. Outcomes of being arrested – mitotic slippage versus mitotic catastrophe

The term mitotic arrest refers to a dividing cell that is halted at one of the mitotic steps. Defects in mitotic checkpoints, perturbations of mitotic spindle dynamics or improper chromosome arrangements such as failure of a single chromosome to attach properly to the mitotic spindle can all result in mitotic arrest (Weaver and Cleveland, 2005; Lambris and Holland, 2017). Of note, antimitotic drugs, such as vinblastine and paclitaxel, are commonly used chemotherapeutic agents that trigger microtubule stabilization and thus induce a mitotic arrest (Gudimchuk and McIntosh, 2021; Cheng and Crasta, 2017; Florian and Mitchison, 2016). Prolonged mitotic arrest leads to either mitotic catastrophe or mitotic slippage (see figure). Mitotic catastrophe refers to a type of cell death specifically occurring during mitosis (Sorokina et al., 2017; Vitale et al., 2011). Here, the delay in strict mitotic timing, as well as premature or inappropriate entry of cells into mitosis, result in alterations of the defined sequence of events and induce cell death, the desired outcome of antimitotic drugs (Diaz-Moralló et al., 2013; Tischer and Gergely, 2018). Mitotic slippage designates cells that exit mitosis after mitotic arrest without proper chromosome segregation; this commonly results in a tetraploid progeny (Cheng and Crasta, 2017; Sinha et al., 2019).



chromatin arms during mitotic entry (Misulovin et al., 2018), exacerbates mitotic errors and induces CIN (Ohbayashi et al., 2007; Haarhuis et al., 2013). It has been shown that WAPL and its binding partner sister chromatid cohesion protein PDS5 homolog B (PDS5B) are lysosomal substrates as their protein levels significantly increase upon inhibition of lysosome acidification in mitotic cells (Almacellas et al., 2021). Furthermore, p62 has been shown to bind PDS5B and WAPL, suggesting that selective autophagy mediates their degradation during mitosis and so contributes to the prevention of CIN (Fig. 2) (Almacellas et al., 2021). Identification of SARs that operate during mitosis together with a large-scale proteomic analysis of mitotic cells to identify novel autophagic substrates might improve our understanding of the regulatory mechanisms involved in mitotic progression, as well as

the contribution of both non-selective and selective autophagy in the control of chromosome segregation.

### Mitochondria

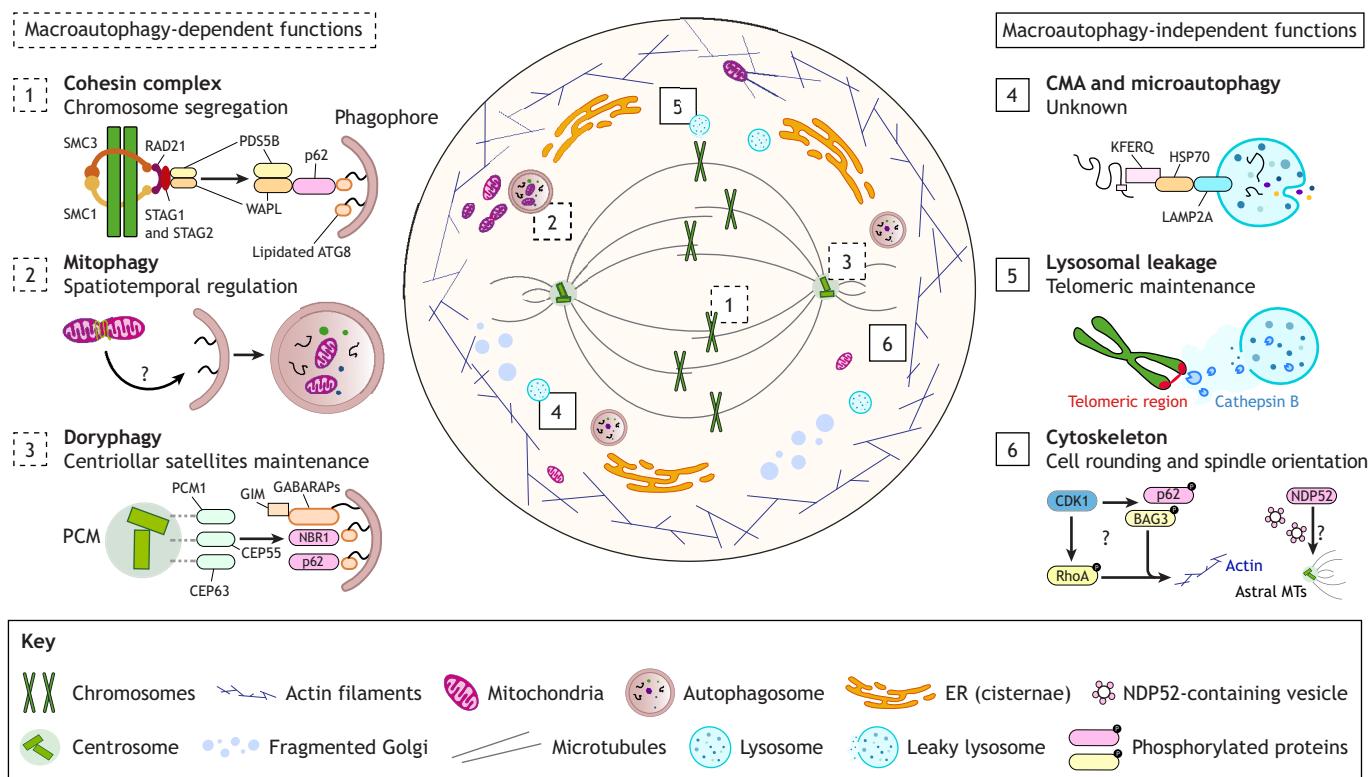
Mitophagy, one of the well-recognized selective autophagy routes for the degradation of mitochondria, serves as a quality-control mechanism for cell homeostasis and has been extensively studied in the context of damaged mitochondria in interphase (Chen et al., 2020; Onishi et al., 2021). The targeting of damaged mitochondria for degradation involves the function of the PTEN-induced putative kinase 1 (PINK1) and the E3-ubiquitin ligase Parkin. Accumulation of these proteins at the mitochondrial surface serves as a signal for their autophagy-dependent degradation (Onishi et al., 2021). Interestingly, in interphase, PINK1–Parkin-dependent mitophagy of damaged mitochondria hinders cells from entering mitosis through the mitochondrial targeting of the serine/threonine-protein kinase TBK1, preventing its localization to centrosomes for mitotic spindle assembly (Doménech et al., 2015; Esteban-Martínez et al., 2015). During mitosis, however, mitophagy has been shown to occur after mitotic arrest release, but the underlying signalling mechanisms and its biological significance remain obscure (Fig. 2) (Liu et al., 2009). One unexplored possibility is that the fittest mitochondria at mitotic entry prevail in order to provide the daughter cells with the necessary energy to restore their metabolic capacity. Therefore, mitophagy during cell division might not be restricted to the removal of damaged mitochondria and might be regulated by an alternative signalling pathway, whose identity remains to be revealed.

### Centrosome integrity

Centrosomes are formed by two centrioles surrounded by a dense protein matrix named pericentriolar matrix (PCM) and are the centre of microtubule nucleation during spindle assembly (Bettencourt-Dias and Glover, 2007). Therefore, centrosome integrity ensures precise chromosome segregation and supports genomic stability. Selective degradation of centriolar satellites by autophagy, named doryphagy, has recently been shown to sustain centrosome function and organization (Holdgaard et al., 2019). This study demonstrated that the autophagic machinery targets the satellite organizer pericentriolar material 1 (PCM1) through a direct interaction with GABARAP and GABARAPL2. The authors report a central role for autophagy in mitotic cells, as autophagy deficiency results in the accumulation of abnormally voluminous centriolar satellites, inducing a dysregulation of centrosome organization and mitotic failure (Holdgaard et al., 2019). Other studies have implicated PCM1 in the control of starvation-induced autophagy, suggesting a bidirectional regulation of centriolar integrity and autophagy in both interphase and mitotic cells (Joachim et al., 2015; Joachim et al., 2017).

### Midbody ring

The involvement of autophagy in the degradation of midbody ring remnants (MRRs) at cytokinesis is by far its best-characterized role in cell division (Pohl and Jentsch, 2009; Isakson et al., 2013; Sardina et al., 2020). Degradation of MRRs is a post-abscission event that depends on a correct autophagic flux during cytokinesis



**Fig. 2. Lysosome-centric view of a mitotic cell.** Lysosome-dependent degradation safeguards mitotic progression with pleiotropic functions. Upon mitotic entry, selective macroautophagy has been demonstrated for the degradation of specific cargos, such as WAPL and PDS5B, both proteins associated with the cohesin complex (1), mitochondria (2), or centriolar satellites through PCM1, CEP55 and CEP63 (3) (highlighted with dashed outlines). In addition, both lysosomes and SARs play a role in the correct orchestration of mitotic progression independently of macroautophagy (solid outlines). Lysosomal leakage supports telomeric maintenance to prevent chromosomal instability (4). Interestingly, other types of autophagy, such as microautophagy and CMA, might also deliver substrates to the lysosomes (5), but their role in mitosis is still unclear. Finally, SARs such as p62 and NDP52 are involved in the remodelling of the actomyosin cortex during cell rounding (6).

(Pohl and Jentsch, 2009). Defective degradation of MRRs has been suggested to be involved in the regulation of cell polarity, proliferation and stemness (Peterman and Prekeris, 2019). At least four autophagic receptors have been implicated in this process: FYVE and coiled-coil domain-containing protein 1 (FYCO1), neighbour of BRCA1 gene (NBR1), the E3 ubiquitin-protein ligase TRIM17 and optineurin (OPTN). FYCO1, a Rab7 effector that binds to LC3 proteins, has been shown to recruit LC3-positive membranes around MRRs in early G1 to target them for degradation (Dionne et al., 2017). Silencing of the SAR OPTN increases the activity of Polo-like kinase 1 (PLK1), an important cell-cycle regulator that activates the APC/C, and thus induces abscission failure and multinucleation (Kachaner et al., 2012). Interaction of NBR1 with the centrosomal protein 55 (CEP55) has been shown to ensure MRR removal (Kuo et al., 2011). TRIM17 has also been shown to selectively trigger autophagy-dependent degradation of MRRs (Mandell et al., 2016). Autophagy remains a dynamic and fast-evolving field of research as suggested by the constant identification of new autophagic receptors and the discovery that SARs can act through canonical as well as non-canonical autophagy (Zellner et al., 2021; reviewed in Gubas and Dikic, 2022; Kirkin and Rogov, 2019).

### **Microautophagy and CMA in cell division – more questions than answers**

Although macroautophagy is the most-studied autophagic process, CMA and microautophagy also contribute to cellular homeostasis by transferring substrates to the lysosomes for degradation. During microautophagy, the lysosome directly engulfs substrates through invagination of the lysosomal membrane. Microautophagy like macroautophagy has been classified as non-selective and selective, and has been shown to participate in metabolic adaptation, organelle remodelling and quality control (reviewed in Li and Hochstrasser, 2020; Schäfer et al., 2020). Selective degradation of nuclear components by microautophagy has been characterized in yeast (Mijaljica and Devenish, 2013; Mochida et al., 2015). Moreover, during ER stress, parts of the ER are degraded by selective microERphagy (Schäfer et al., 2020). Interestingly, although extensive ER remodelling at mitotic entry has been observed (Carlton et al., 2020; Bergman et al., 2015), the potential contribution of autophagy in this process is unknown. In addition, one could speculate that microautophagy might degrade substrates faster than macroautophagy, as it does not require the formation of autophagosomes as transport intermediates. However, the function of microautophagy in mammals is far less understood than in yeast, and whether microautophagy plays a role in mitosis remains unresolved.

In contrast to microautophagy, CMA has been much better characterized. Briefly, CMA substrates contain a KFERQ motif, which allows their recognition by the Hsc70 isoform of the heat-shock chaperone protein HSP70 (reviewed in Arias and Cuervo, 2020). Proteome-wide analysis of proteins bearing this CMA-targeting motifs was recently performed (Kirchner et al., 2019), and proteins involved in mitosis [Gene Ontology (GO) term ID 0000278] were identified, suggesting a possible role for CMA in mitotic progression. Further studies are needed to better characterize microautophagy and CMA in mitotic cells to shed light on their possible contribution to cell division. It is important to note that lysosomes and autophagy, although intrinsically related, have also independent roles in a variety of cellular processes. Thus, studies deciphering these processes would be helpful in resolving the current controversy regarding their possible function in mitotic progression.

### **Autophagy-independent mitotic functions of lysosomes**

Lysosomes are acidic organelles that act in several autophagy-independent processes depending on their intracellular localization, such as plasma membrane repair, antigen presentation, lysosome leakage and apoptotic cell death (Pu et al., 2016). As noted above, lysosomes are crucial organelles for the maintenance of cellular homeostasis, and alterations of lysosome function have been described in a myriad of pathologies, including lysosome storage diseases, and also cancer, neurodegenerative and cardiovascular diseases (reviewed in Ballabio and Bonifacino, 2020). Lysosomes contain a complex enzymatic cocktail that enables the degradation of any biological material. For this reason, permeabilization of the lysosomal membrane is a hazardous event, owing to the release of hydrolytic enzymes into the cytosol, which activates cell death pathways, such as apoptosis, necroptosis, pyroptosis and ferroptosis (Aits and Jäättelä, 2013). Below, we discuss the function of lysosomes in macroautophagy-independent processes during mitosis.

#### **Lysosome leakage**

Lysosome quality control includes either lysosome repair or lysophagy, which are crucial for the maintenance of intracellular homeostasis (Hung et al., 2013; Yao et al., 2021). Lysophagy is the selective clearance of damaged and dysfunctional lysosomes, which is signalled by the recruitment of galectin-3 and tripartite motif-containing protein 16 (TRIM16) to the site of lysosomal membrane permeabilization to prompt the autophagy machinery to engulf damaged lysosomes (Maejima et al., 2013; Chauhan et al., 2016; Aits et al., 2015). Upon lysosomal membrane permeabilization, the fast recruitment of galectins to the site of leakage is essential to counteract the deleterious release of lysosomal hydrolases into the cytosol, the activation of cell death pathways and mitotic catastrophe (Jia et al., 2020). However, a recent study demonstrated that controlled lysosome leakage in mitotic cells protects against chromosome missegregation (Hämäläistö et al., 2020). The authors demonstrated that in pro-metaphase, lysosomes leak in proximity to the DNA, and that this occurs preferentially at the telomeric and not at the centromeric region of chromosomes. Telomeres are protective caps of the chromosomes that come in close proximity when chromosomes are aligned at metaphase plate (de Lange, 2018). End-to-end fusion between sister chromatids and telomere shortening are known triggers of chromosome missegregation (Stroik and Hendrickson, 2020). Hämäläistö et al. demonstrated that the release of cathepsin B by leaky lysosomes promotes the specific cleavage of histone H3 and assists in untangling fused telomeres of aligned chromosomes (Hämäläistö et al., 2020). Accordingly, inhibition of cathepsin B activity induced telomere-mediated chromosome missegregation and triggered CIN as observed by an increase in micronuclei frequency (Box 1) (Hämäläistö et al., 2020). Despite these insights into the mechanisms underlying the role of mitotic lysosome leakage, several questions remain unanswered, such as how cathepsin B is selectively released from leaky lysosomes or how a controlled lysosomal leakage is regulated to prevent mitotic catastrophe (Box 2 and figure therein). Nonetheless, there is evidence that the degree of lysosome leakage and the nature of the lysosomal enzyme can determine the outcome (Kågedal et al., 2001), suggesting that limited lysosomal leakage might contribute to cell homeostasis. In addition, the lack of sensitive detection tools prior to development of the galectin puncta assay (Aits et al., 2015) hindered the acquisition of solid data on limited transient lysosomal leakage and its possible cellular functions.

### Lysosome trafficking

Lysosome function and positioning are intrinsically linked in interphase cells, and recent studies have pointed out their mutual regulation (Jia and Bonifacino, 2019; Lin et al., 2022). Indeed, peripheral lysosomes have been shown to play a role in plasma membrane repair and extracellular matrix acidification, whereas perinuclear lysosomes near the microtubule-organizing centre (MTOC) are suggested to have higher degradative capacity (Pu et al., 2016). Lysosomal trafficking occurs via microtubules, which serve as molecular tracks to arrange and deliver organelles to specific intracellular localizations (Lie and Nixon, 2019; Gudimchuk and McIntosh, 2021). Retrograde transport of lysosomes involves the dynein–dynactin motor complex coupled to adaptor proteins (Cabukusta and Neefjes, 2018). Anterograde transport of lysosomes is mediated by kinesins, specifically KIF5B, a member of kinesin-1 family, and KIF1B, a member of the kinesin-3 family. Both proteins can engage with Arl8b GTPases and the multi-subunit protein complex BLOC-one-related complex (BORC) to transport lysosomes from the minus-end to the plus-end of microtubules (Pu et al., 2016; Pu et al., 2017). The FYCO1–Rab7 complex also mediates microtubule-based transport of lysosomes (Pankiv et al., 2010), but its directionality has been shown to depend on the phosphorylation status of LC3B (Nieto-Torres et al., 2021). Whether Rab7 and Arl8b GTPases bind to the same population of lysosomes is unknown, and therefore the specificity of these motors is still under study. During mitosis, cell polarity changes, and microtubules reorganize to form the mitotic spindle. Interestingly, although it is unknown whether FYCO1-dependent lysosomal transport is involved in mitotic progression, depletion of BORC-associated motors significantly delays mitotic progression and increases mitotic errors, inducing CIN (Almacellas et al., 2021). This study proposes that lysosomes positioning contributes to mitotic accuracy. Importantly, mitotic poisons, such as paclitaxel and vincristine, have been investigated for their use in cancer therapy (Tischer and Gergely, 2018) as they are able to arrest mitotic cells by disrupting the cytoskeleton dynamics (Box 1). Nonetheless, it is now clear that apart from inducing mitotic arrest, these drugs strongly affect overall membrane trafficking, specifically the positioning and therefore function of vesicles, such as lysosomes. Indeed, vincristine has been shown to induce dramatic lysosomal changes (Groth-Pedersen et al., 2007), therefore employing these types of drugs should be met with caution when studying lysosomes.

### Autophagy-independent functions of ATG and SAR proteins during cell division

Although the historical characterization of protein function in specific pathways is crucial for our current understanding of cell biology, it might also have led to a misattribution of phenotypes to specific cellular pathways, as proteins can act in multiple intracellular processes. Indeed, despite a good understanding of their autophagic functions, several ATG proteins and SARs have more recently been described to have a role in other cellular processes (reviewed in Mauthe and Reggiori, 2016). Here, we briefly summarize the mitotic phenotypes described upon depletion of autophagic proteins (Table 1).

#### Initiation and nucleation

Several proteins involved in the early steps of autophagy have been implicated in mitotic phenotypes. Indeed, after release of thymidine block, the chemical inhibition of ULK1/2 kinase induced aneuploidy, mitotic delay and spindle defects (Ji et al., 2020). Accordingly, genetic depletion of ULK1 led to an increase of

mitotic timing and multipolar spindles in U2OS cells (Holdgaard et al., 2019). Another study pinpoints the importance of ULK1 for correct chromosome segregation, and shows that knockout of ULK1, ATG13 or FIP200 increases mitotic errors and aneuploidy (Yuan et al., 2019). However, the authors attribute this phenotype to the ULK1-dependent phosphorylation of Mad1 (MAD1L1) S546, which is required for its recruitment to the kinetochores to support spindle assembly checkpoint (SAC) (Yuan et al., 2019). In addition, the PI3KC3 complex 1 components VPS34, VPS15 and Beclin-1 have been linked to abscission defects and MRR degradation (Sagona et al., 2010; Thoresen et al., 2010; Pohl and Jentsch, 2009). To what extent such effects occur through autophagy impairment or linked to PI3P production for other cellular processes remains unclear.

### Elongation

Depletion of ATG7 has been shown to induce the accumulation of MRRs both in U2OS and mouse embryonic fibroblast (MEF) cells, suggesting its involvement in autophagy-dependent MRR removal (Pohl and Jentsch, 2009). Moreover, loss of ATG7 phenocopies the depletion of GABARAPL2 in mitotic doryphagy, suggesting that centrosome integrity is indeed mediated by autophagy (Holdgaard et al., 2019). Finally, ATG5, another protein involved in the lipidation machinery, has been found to prevent mitotic errors in U2OS and MEF cells, suggesting a basal role of autophagy in restraining CIN (Almacellas et al., 2021).

### SARs and other accessory proteins

Several studies have observed altered mitotic phenotypes upon depletion of SARs and other accessory proteins, such as disturbed cell rounding or defective MRR removal. Cell rounding is necessary for mitotic entry and relies on a rapid modification of the mechanical properties of the actomyosin cortex (Stewart et al., 2011). Such changes are triggered by CDK1 and mediated by the Ras homolog family member A (RhoA) GTPase, among others (Fig. 2) (Chircop, 2014). A defective cell rounding leads to impairment of spindle assembly and a delay in mitotic progression (Lancaster and Baum, 2014; Lancaster et al., 2013). Both p62 and the nuclear dot protein 52 kDa (NDP52; also known as CALCOCO2) participate in cell rounding at the onset of mitosis (Yu et al., 2019; Luthold et al., 2021; Fuchs et al., 2015; Belaid et al., 2013). Whether the function of SARs in cytoskeleton reorganization is linked to autophagy or related to autophagy-independent functions remains unclear (Table 1).

As noted above, different studies have uncovered functions for p62, FYCO1, NBR1 and TRIM17 in MRR degradation after cytokinesis (Pohl and Jentsch, 2009; Dionne et al., 2017; Kuo et al., 2011; Mandell et al., 2016). Phosphorylation of OPTN by PLK1 has been proposed to regulate cell abscission through its interaction with a myosin phosphatase complex (Kachaner et al., 2012). Finally, UVRAg, a component of the PI3KC3 complex 2 (Liang et al., 2006; Matsunaga et al., 2009; Takahashi et al., 2007; Zhong et al., 2009), plays a critical role in maintaining chromosomal stability. Briefly, UVRAg controls DNA-damage response through DNA-dependent protein kinase (DNA-PK; also known as PRKDC) and non-homologous end joining (NHEJ) repair, probably during S-phase, and it is also associated with centrosomes stability through its interaction with the centrosomal protein 63 kDa (CEP63), thus preventing aneuploidy (Zhao et al., 2012).

Over the past few years, many studies have uncovered a link between the genetic or chemical inhibition of ATGs or

**Table 1.** Functions attributed to autophagic proteins and SARs in cell division

	Protein symbol (human)	UniProt ID	Function in cell division	References
<b>Initiation and nucleation</b>				
<b>ULK complex</b>	ULK1, ULK2	Q75385, Q8IYT8	Aneuploidy Chromosome segregation Mitotic timing Mitotic spindle organization	Yuan et al., 2019; Holdgaard et al., 2019; Ji et al., 2020
	ATG13	Q75143	Chromosome segregation	Yuan et al., 2019
	FIP200	Q8TDY2	Chromosome segregation	Yuan et al., 2019
	ATG101	Q9BSB4	ND	
<b>ATG2, ATG9 and WIPIs</b>	ATG2A, ATG2B	Q2TAZ0, Q96BY7	ND	
	ATG9A, ATG9B	Q7Z3C6, Q674R7	ND	
	WIP1–WIPI4	Q5MNZ9, Q9Y4P8, Q5MNZ6, Q9Y484	ND	
<b>PI3K complex 1</b>	PIK3C3 (VPS34)	Q8NEB9	Cell abscission	Sagona et al., 2010; Thoresen et al., 2010
	PIK3R4 (VPS15)	Q99570	Cytokinesis	Thoresen et al., 2010
	BECN1	Q14457	Chromosomal instability Midbody removal	Mathew et al., 2007; Pohl and Jentsch, 2009
	ATG14L	Q6ZNE5	ND	
<b>Elongation</b>				
<b>ATG8 Ubl-CS</b>	LC3A–LC3C, GABARAP, GABARAPL1/2	Q9H492, Q9GZQ8, Q9BXW4, O95166, Q9H0R8, P60520	Multipolar spindles (GABARAPL2 specific)	Holdgaard et al., 2019
	ATG7	Q95352	Mitotic timing Mitotic centrosome fragmentation Micronuclei Midbody removal	Holdgaard et al., 2019; Pohl and Jentsch, 2009
	ATG3	Q9NT62	ND	
	ATG4A–ATG4D	Q8WYN0, Q9Y4P1, Q96DT6, Q86TL0	ND	
<b>ATG12 Ubl-CS</b>	ATG12	Q94817	ND	
	ATG7	Q95352	See above	
	ATG10	Q9H0Y0	ND	
	ATG16L1	Q676U5	ND	
	ATG5	Q9H1Y0	Chromosome segregation	Almacellas et al., 2021
<b>SARs</b>	SQSTM1 (p62)	Q13501	Cell rounding (actomyosin cortex) Midbody removal	Yu et al., 2019; Luthold et al., 2021; Fuchs et al., 2015; Pohl and Jentsch, 2009
	CALCOCO2 (NDP52)	Q13137	Cell rounding (actomyosin cortex)	Yu et al., 2019; Luthold et al., 2021; Fuchs et al., 2015
	FYCO1	Q9BQS8	Midbody removal	Dionne et al., 2017
	NBR1	Q14596	Midbody removal	Kuo et al., 2011
	TRIM17	Q9Y577	Midbody removal	Mandell et al., 2016
	OPTN	Q96CV9	Cell abscission	Kachaner et al., 2012
<b>Others</b>	DFCP1	Q9HBF4	ND	
	UVRAG	Q9P2Y5	Chromosome segregation Mitotic spindle organization Centrosome integrity	Zhao et al., 2012
	PCM1	Q15154	Doryphagy	Holdgaard et al., 2019
	RUBCN	Q92622	ND	
	RUBCNL (PACER)	Q9H714	ND	

ND, not determined; Ubl-CS, Ubl conjugation system.

SARs and CIN, supporting a positive role of autophagy in ensuring proper cell division (Table 1). However, considering the time required for siRNA-dependent depletion of specific proteins, the length of chemical treatments and the short timing of mitosis, as well as any alternative function of these proteins beyond autophagy, it is difficult to envisage to what extent the effects observed in dividing cells might reflect residual effects from interphase or other cellular processes. Therefore, it remains important to clarify the precise mechanisms by which these autophagic proteins regulate mitosis and whether inhibition of mitotic autophagy is the main factor that causes CIN or additional pathways are involved.

### Conclusions and perspectives

For a long time, the UPS was considered the only mitotic degradative system essential to guarantee the scheduled progression of mitosis. However, the recent identification of autophagic proteins and lysosomes as important factors that control mitotic progression has opened a new avenue to explore the mechanisms safeguarding genomic stability. Given that faithful chromosome segregation is vital for cell proliferation and genome conservation, it might be expected that both degradative systems collaborate to support cell division. However, to date it is still unclear whether UPS and lysosomes can compensate for each other in the context of mitosis. Given the complex arrays of SARs

described in interphase, research focused on deciphering mitotic functions of SARs would greatly improve our knowledge of the degradation routes operating in cell division.

Although a role for autophagy and lysosomal degradation in mitotic cells has been recently demonstrated, it is still not clear what are the sources of membrane for the nucleation and expansion of the phagophore during cell division. In mitosis, cells rapidly alter their volume and surface topology with little time for *de novo* membrane synthesis to accommodate such changes. Instead, cells employ shaping, relocation and removal of existing membranes to support cell division (reviewed in Carlton et al., 2020). Indeed, participation of endocytosis, endocytic recycling and lysosome exocytosis has been described to accommodate such mitotic membrane requirements (Boucrot and Kirchhausen, 2007; Tacheva-Grigorova et al., 2013; Nugues et al., 2018 preprint). As autophagy initiation sites mostly form at ER exit sites (ERES), and intensive ER remodelling occurs during mitosis (Zhang and Hu, 2016; Maeda et al., 2020), a reduced capacity of generating *de novo* autophagosomes is to be expected. Hence, an unresolved question is still whether mitotic autophagosomes correspond to interphase-synthesized vesicles. However, this idea neglects that autophagosome initiation sites are diverse, and membranes from different organelles can contribute to phagophore nucleation and expansion, including the plasma membrane (Moreau et al., 2012), recycling endosomes and the Golgi (Lamb et al., 2013; Puri et al., 2018), as well as the recently described hybrid pre-autophagosomal structure (HyPAS) (Kumar et al., 2021). Further characterization of mitotic autophagic vesicles, as well as the identification of their substrates are thus needed to improve our understanding of mitotic autophagy.

Mitotic poisons are widely used in the clinic to treat cancer, but unfortunately, they also cause highly detrimental secondary effects. Indeed, as microtubule-stabilizing agents, mitotic poisons have an impact on the dynamics and function of organelles, which to date has been mostly disregarded. Nonetheless, alterations in lysosome activity have been correlated with an increase in CIN, which contributes to tumour heterogeneity and anticancer drug resistance. Considering the multiple functions of lysosomes and our limited understanding of autophagy mechanisms in the context of mitosis, future studies in this area are anticipated to lead to the development of novel antiproliferative therapeutic strategies.

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