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CELL SCIENCE AT A GLANCE

# Ambra1 at a glance

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## ABSTRACT

The activating molecule in Beclin-1-regulated autophagy (Ambra1), also known as autophagy/Beclin-1 regulator 1, is a highly intrinsically disordered and vertebrate-conserved adapter protein that is part of the autophagy signaling network. It acts in an early step of mammalian target of rapamycin complex 1 (mTORC1)-dependent autophagy by favouring formation of the autophagosome core complex. However, recent studies have revealed that Ambra1 can also coordinate a cell response upon starvation or other stresses that involve translocation of the autophagosome core complex to the endoplasmic reticulum (ER), regulative ubiquitylation and stabilization of the kinase ULK1, selective mitochondria removal and cell cycle downregulation. Moreover, Ambra1 itself appears to be targeted by a number of regulatory processes, such as cullin-dependent degradation, caspase cleavage and several modifications, ranging from phosphorylation to ubiquitylation. Altogether, this complex network of regulation highlights the importance of Ambra1 in crucial physiological events, including metabolism, cell death and cell division. In addition, Ambra1 is an important regulator of embryonic development, and its mutation or inactivation has been shown to correlate with several pathologies of the nervous system and to be involved in carcinogenesis. In this Cell Science at a Glance article and the accompanying poster, we discuss recent advances in the Ambra1 field, particularly the role of this pro-autophagic protein in cellular pathophysiology.

**KEY WORDS: Autophagy, Cell cycle, Mitochondria, Nervous system, Cancer biology**

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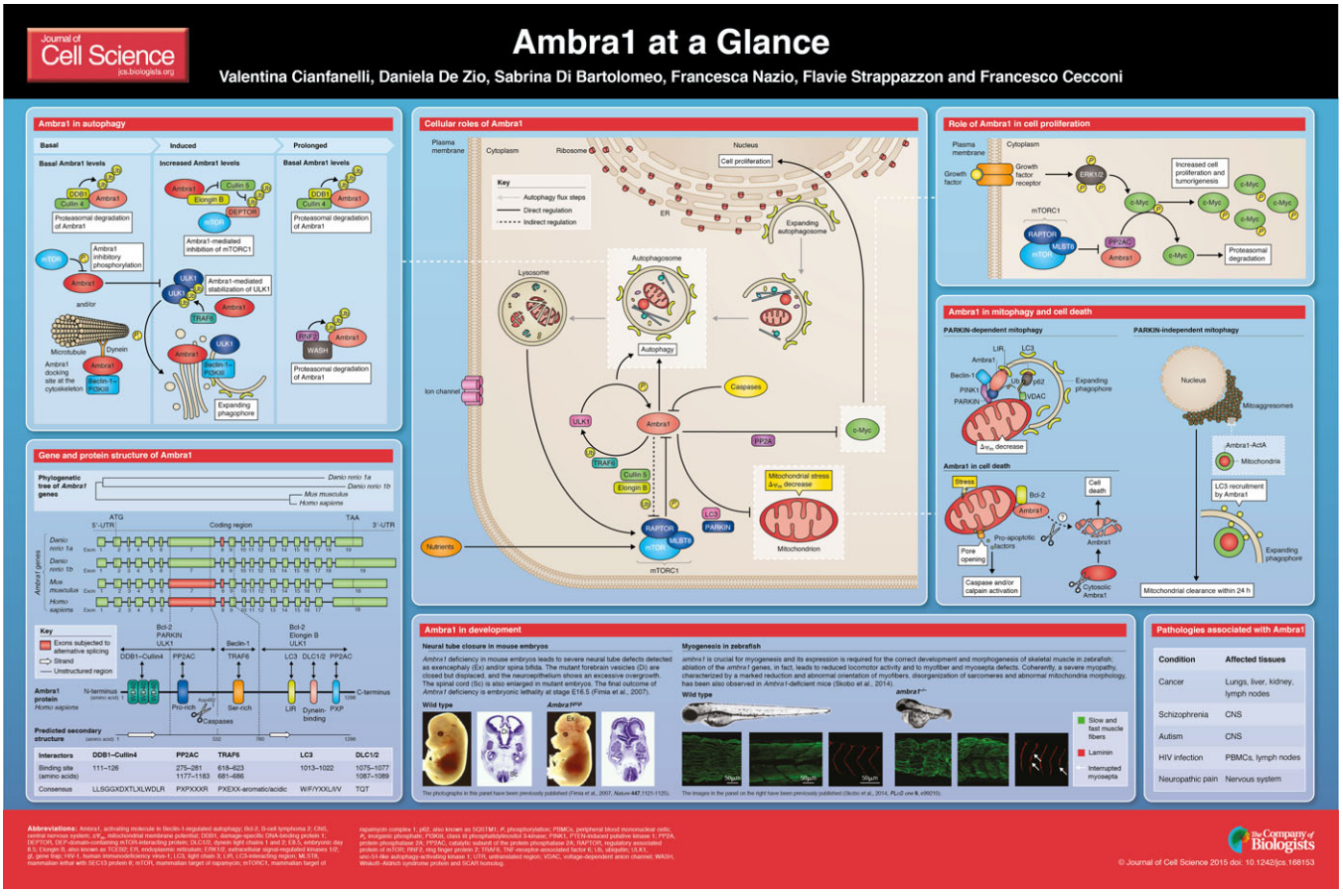
## Introduction

Macroautophagy (hereafter referred to as autophagy) is a complex cellular process that is involved in the lysosome-mediated degradation of damaged or old organelles, protein aggregates and long-lived proteins (Boya et al., 2013). Under standard conditions – such as when



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**Box 1. *Ambra1* genes and isoforms**

As a consequence of the fish-specific whole-genome duplication occurring after the divergence of the fish and tetrapod lineage (Meyer and Van de Peer, 2005), *AMBRA1* has two counterparts in zebrafish (*Danio rerio*) – the paralog genes *ambra1a* and *ambra1b* (see poster) (Benato et al., 2014). Interestingly, *ambra1a* and *ambra1b* are not functionally redundant (see below), suggesting that together they accomplish the multiple roles of the orthologous gene present in humans (Benato et al., 2014; Skobo et al., 2014).

Unlike the zebrafish genes, the mouse and the human *AMBRA1* genes contain only 18 exons, with the last exon (exon 18 in poster) bearing a longer coding region relative to that of the zebrafish counterpart (see poster). This discrepancy in the number or length of the last exon(s) of the gene among different species accounts for the low sequence identity between the C-terminal regions of mammalian and zebrafish Ambra1 proteins.

Apart for the extreme C-terminal region, the Ambra1 protein sequence – as well as its organization into domains, which includes three WD40 domains at the N-terminus (N-terminus) of the protein (see poster) – is highly conserved among mammals and zebrafish. WD40-domain proteins coordinate multi-protein complex assembly and typically constitute a rigid scaffold for protein–protein interactions (Stirnimann et al., 2010). Other regions of interest in the Ambra1 sequence are proline and serine (Pro/Ser)-rich regions, the function(s) of which are still unknown. Also, several protein-binding motifs have been identified in the Ambra1 sequence (see poster). Apart from these domains and motifs, Ambra1 is mainly characterized by structural disorganization (see main text).

nutrients are abundant within the cell – protein synthesis proceeds incessantly or cells might divide, and a series of cellular events regulated by the autophagy signaling network ensure quality control of cellular components and maintain cellular homeostasis. However, in the context of a vast number of stress stimuli, ranging from starvation to hypoxia or DNA damage, autophagy constitutes a key pro-survival response, thus allowing adaptation to unfavourable conditions (Abada and Elazar, 2014; Boya et al., 2013; Choi et al., 2013).

Comprehensively, the upstream autophagy signaling network includes mammalian target of rapamycin complex 1 (mTORC1), a crucial metabolic switch that normally inhibits autophagy, and the 'core autophagy machinery', mainly comprising four macromolecular complexes, which have been extensively reviewed elsewhere (see Abada and Elazar, 2014; Boya et al., 2013). Briefly, these are the unc-51-like autophagy-activating kinase 1 (ULK1) kinase complex, the class III phosphatidylinositol 3-kinase (PI3KIII) complex, the ubiquitin-like conjugation system – mainly comprising autophagy related gene 12 (ATG12) and light chain 3 (LC3) – and transmembrane proteins, such as mammalian autophagy-related gene 9 (ATG9; also known as ATG9A) (Abada and Elazar, 2014).

ULK1 and PI3KIII activate the early steps of autophagy by promoting the formation of a double-membraned organelle, the autophagosome, that engulfs autophagy substrates (such as entire organelles and long-lived proteins) and delivers them to the lysosome, where they are degraded by lytic enzymes (Abada and Elazar, 2014). One of the main regulators of the autophagy process is activating molecule in Beclin-1-regulated autophagy1 (Ambra1) (Fimia et al., 2007), recently renamed by the HUGO Nomenclature Committee as autophagy/Beclin-1 regulator 1.

Ambra1 is an intrinsically disordered protein (IDP) (discussed below), with a molecular mass of ∼130 kDa. Indeed, the intrinsic disorder of Ambra1 accounts for the great plasticity of this protein, making it an excellent scaffold-molecule candidate that is able to coordinate several intracellular processes with autophagy (Mei et al., 2014; Peng et al., 2013). In fact, a number of interaction partners of Ambra1 have been identified and highlight the involvement of Ambra1 in autophagy, apoptosis and the cell cycle (see poster).

In the context of pathology, *AMBRA1* has, initially, been implicated in impaired embryogenesis and found to be involved in mouse congenital malformation and human neurological disorders (Dere et al., 2014; Fimia et al., 2007; Heinrich et al., 2013, Marinelli et al., 2014; Rietschel et al., 2012; Skobo et al., 2014; Vázquez et al., 2012). Beyond this point, *AMBRA1* is a bona fide tumor suppressor gene and has been found to be mutated in a significant percentage of human tumors of various tissues (Cianfanelli et al., 2015c). Taken together, these findings indicate that Ambra1 is likely to be an important target for pharmacological manipulations in several pathologies. This Cell Science at a Glance article will summarize the recent progress in the field that has illustrated the biological relevance of Ambra1.

## Ambra1 (un)structure

Ambra1 is a protein comprising 1300 amino acid residues, and the gene that encodes it (*AMBRA1*), located on chromosome 11 in humans, comprises 18–19 exons, some of which are predicted or have been shown to undergo alternative splicing, giving rise to various transcript variants [Ensembl (Benato et al., 2014)] (Box 1).

Interestingly, Ambra1 is mainly unstructured and is characterized by regions of presumed intrinsic disorder (intrinsically disordered regions, IDRs) (Dyson and Wright, 2005) that are found along its entire sequence (except for the two small regions predicted to be organized into β-strands; see poster). Proteins bearing IDRs, called IDPs, are abundant in the proteome and participate in many different biological processes, mainly by regulating protein–protein interaction networks (Uversky and Dunker, 2010). Indeed, the flexibility of IDRs enables them to undergo conformational changes to form diverse interaction surfaces that are complementary to different proteins. Also, protein-interaction motifs within the same IDR can simultaneously bind to different partners, turning IDPs into molecular 'hubs' that are involved in multiple interactions with unrelated partners. The great number and the functional characterization of Ambra1 interactors (discussed below and in Cianfanelli et al., 2015a) clearly illustrates that this is the case here.

It has been recently demonstrated that a considerable number of autophagy regulators and effectors bear IDRs, often enriched in regions of protein–protein interaction (Mei et al., 2014; Peng et al., 2013). It has also been shown that the IDRs of Beclin-1 and Atg1 (the yeast ortholog of the human ULK1 complex) fold upon binding to their respective interactors – B-cell lymphoma 2 (Bcl-2) and autophagy-related gene 13 (Atg13) – with these folding events being functional to the dynamic regulation of Beclin-1–Bcl-2 and Atg1–Atg13 complexes (Mei et al., 2014; Stjepanovic et al., 2014).

Intriguingly, proteins with large IDRs show lower conservation across species, and consequently, homologs are difficult to identify based solely on sequence. In line with this, the disordered nature of Ambra1 could account for the lack of homologs in insects, worms and yeast identified thus far. This implies that equivalent functions of Ambra1 in these organisms are performed either by proteins that share very low, undetectable sequence identity to the mammalian protein or by completely different proteins (functional orthologs).

Despite the lack of domains, the Ambra1 sequence has been functionally annotated through the identification of its numerous interactors and, in most cases, of the corresponding interacting motifs and regions (see poster, and discussed below). Furthermore, comparison of the coding and protein sequences of Ambra1 suggests that the composition of its interacting motifs changes upon splicing (see poster).

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### Ambra1-mediated regulation of autophagy

Under basal conditions, Ambra1, together with Beclin-1 and PI3KIII, is bound to the dynein light chains (DLC1 and DLC2) of the dynein motor complex (Di Bartolomeo et al., 2010). Upon autophagy induction, ULK1-mediated phosphorylation releases Ambra1 from the dynein complex and results in its translocation, together with Beclin-1 and PI3KIII, to the endoplasmic reticulum (ER), where autophagosomes form. Recently, we have shown that Ambra1 regulates the activity and the stability of ULK1, pointing to a broader role of Ambra1 in ensuring the execution of the autophagy program (Nazio et al., 2013). With regard to the molecular mechanism, in the early stages after autophagy induction, Ambra1 promotes the ubiquitylation of ULK1 through Lys63-linked ubiquitin chains; this modification is essential for the self-association of ULK1 and is mediated by the E3 ligase TNF receptor associated factor 6 (TRAF6), which interacts with the Ambra1–ULK1 complex. This mechanism represents a positive-feedback loop, whereby Ambra1 helps to fine-tune the autophagic response by enhancing the signaling capacity of ULK1. Moreover, Lys-63-linked ubiquitylation of ULK1 is prevented through mTORC1-mediated phosphorylation of Ambra1 at serine residue 52. Under conditions that favor mTORC1 activation, Ambra1 is thus kept in an inactive state by this phosphorylation event (Nazio et al., 2013).

In addition to our study above, it has also been proposed that Ambra1 acts as an essential co-factor for other E3 ligases. For instance, a newly identified cullin E3 ligase complex, cullin 5, has recently been observed to be associated with Ambra1 (Antonioli et al., 2014). Here, in the early stages of autophagy induction, Ambra1 interacts with elongin B (also known as TCEB2) to suppress cullin 5 activity, which then allows the stabilization of DEP-domain-containing mTOR-interacting protein (DEPTOR), a starvation-inducible inhibitor of mTORC1 activity. Increased expression of DEPTOR is required to establish a negative-feedback loop of mTORC1 to maintain autophagy activation. Furthermore, Ambra1 can act as a substrate receptor for the regulative Lys63-ubiquitylation of Beclin-1 by interacting with a complex of damage-specific DNA-binding protein 1 (DDB1)–cullin-4 and, thus, enhancing the association of Beclin-1 with PI3KIII (Behrends et al., 2010; Jin et al., 2006; Xia et al., 2013).

In addition to its role as a substrate receptor for E3 ligases, Ambra1 also represents a direct substrate for ubiquitylation, and two different E3 ligase complexes have been identified as being able to induce ubiquitin-mediated proteasomal degradation of Ambra1. Firstly, Xia and colleagues have identified a role for a complex comprising ring finger protein 2 (RNF2) and 'Wiskott–Aldrich syndrome protein and SCAR homolog' (WASH) (Xia et al., 2014). In particular, they have found that RNF2 ubiquitylates Ambra1 at Lys45 with Lys48-linked ubiquitin chains; this modification occurs after the induction of autophagy through starvation and results in the suppression of autophagy (Xia et al., 2014). Secondly, the cullin-4–DDB1 complex has also been found to contribute to the ubiquitylation and degradation of Ambra1 (Antonioli et al., 2014). Also, in this case, the degradation of Ambra1 is crucial for the termination of the autophagy response. Interestingly, the activity of both ULK1 and TRAF6 is essential for regulating the interaction between DDB1 and Ambra1, demonstrating the stringent crosstalk among these regulative mechanisms in the initiation and termination of autophagy.

### Selective autophagy – the role of Ambra1 in mitophagy

#### PARKIN-dependent mitophagy

Damaged mitochondria in which the mitochondrial membrane potential has collapsed ($\Delta\Psi_m$) are subjected to a form of selective autophagy, termed mitophagy. During this process, depolarized mitochondria are ubiquitylated and then recruit p62 (also known as SQSTM1; an autophagy adaptor involved in linking polyubiquitylated protein aggregates to the autophagic machinery). Next, these mitochondria are transported along microtubules to the perinuclear region, where they form rough aggregate structures termed mito-aggresomes (Lee et al., 2010; Okatsu et al., 2010; Vives-Bauza et al., 2010). This step shortly precedes their lysosomal degradation. The E3 ubiquitin ligase PARKIN (also known as PARK2) and the serine/threonine kinase PTEN-induced putative kinase 1 (PINK1) regulate mitophagy after mitochondrial damage (Narendra et al., 2008). Here, PINK1 recruits PARKIN together with Beclin-1 to the translocase of the outer membrane (TOM) machinery, located on depolarized mitochondria, for their subsequent removal through mitophagy (Choubey et al., 2014; Bertolin et al., 2013). In this context, the cytosolic pool of Ambra1 interacts with PARKIN to enhance mitochondrial clearance (Van Humbeeck et al., 2011). Furthermore, the Ambra1–LC3 interaction is crucial in order to amplify PARKIN-mediated mitochondrial clearance (Strappazzon et al., 2015).

#### PARKIN-independent mitophagy

During selective autophagy, autophagy receptors play a major role by tethering cargoes (e.g. mitochondria) to the site of engulfing-autophagosomes through their direct interaction with LC3. The autophagy receptor NIX (also known as BNIP3L) mediates the removal of mitochondria during reticulocyte differentiation (Schweers et al., 2007), whereas FUN14-domain-containing 1 (FUNDC1) mediates mitochondrial clearance following hypoxia (Liu et al., 2012). By generating and expressing an organelle-targeted mutant of Ambra1 (Ambra1-ActA), we have discovered that mitochondrial Ambra1 induces (i) relocalization of the mitochondrial network around the nucleus, (ii) depolarization and ubiquitylation of mitochondria and (iii) recruitment of the molecular platform that is necessary to induce functional mitophagy through a PARKIN–p62-independent pathway (Strappazzon et al., 2015). In this context, Ambra1-ActA (see poster) acts as an autophagy receptor and facilitates mitochondrial clearance by transporting damaged mitochondria into autophagosomes through interactions between its LC3-interacting region (LIR) motif and LC3 (see poster). In addition, we have demonstrated that wild-type Ambra1 is also sufficient to restore mitophagy induction in PINK1$^{-/-}$ or PARKIN-defective cells, underpinning the existence of a specific Ambra1-dependent mitophagy pathway (Strappazzon et al., 2015).

### Ambra1 in cell death

A functional deficiency of Ambra1 in mice is typically accompanied by the appearance of a large number of apoptotic cells (Cecconi et al., 2008; Fimia et al., 2007). Subsequently, it has been shown that reduced levels of Ambra1 lead to an increased susceptibility to different apoptotic stimuli and that, following apoptosis induction, Ambra1 is degraded by caspase and calpain proteases (Pagliarini et al., 2012). Moreover, a caspase-resistant form of Ambra1 (Ambra1-D482A) is able to protect cells from apoptosis better than wild-type Ambra1. Taken together, these results highlight a pro-survival effect of the pro-autophagic protein Ambra1. Indeed, cerebellar granule neurons overexpressing Ambra1 are more resistant to trophic factor deprivation than control neurons (Strappazzon et al., 2011).

In fact, there is a complex relationship between autophagy and apoptosis (Maiuri et al., 2007). Usually, proteins that are able to induce cell death can also induce autophagy and vice versa. The well-known anti-apoptotic factor Bcl-2 is a key factor in this crosstalk. Indeed, a dynamic interaction between Ambra1 and Bcl-2

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at mitochondria regulates both Beclin-1-dependent autophagy and apoptosis (Strappazzon et al., 2011). Under normal conditions, a pool of Ambra1 binds preferentially to mitochondria-resident Bcl-2, which inhibits the pro-autophagic activity of Ambra1. Upon the induction of apoptosis, Ambra1 is released from Bcl-2, and most likely degraded by caspases.

### Regulation of cell proliferation through Ambra1

In order to adapt to nutrient deprivation or other cell stresses, a simultaneous regulation of autophagy and cell growth occurs in eukaryotic organisms. First, a plethora of signaling molecules and pathways have been shown to have opposite effects on cell growth and autophagy, supporting the idea that these processes might represent mutually exclusive cell fates (Neufeld, 2012). This reciprocal inhibition between autophagy and cell growth can occur either through direct regulative mechanisms, most of which remain to be determined to date, or through the same signaling pathways that act independently and simultaneously on autophagy and cell growth. Given its central role in integrating environmental signals – such as the presence of nutrients, hormones and growth factors – mTORC1 is a pivotal regulator in this context (Hosokawa et al., 2009; Laplante and Sabatini, 2012). Interestingly, it has recently been shown that Ambra1 is an effector of mTORC1 signaling in both these pathways, as inhibition of mTORC1 results in the activation of Ambra1 in autophagy (see above) and in the downregulation of Ambra1-mediated cell proliferation (Cianfanelli et al., 2015c; Nazio et al., 2013).

In the presence of growth factors, phosphorylation of the proto-oncogene myelocytomatosis oncogene cellular homolog (c-Myc) at serine residue 62 results in its stabilization and increased cell proliferation (Sears et al., 2000). Recently, the direct binding of Ambra1 to the catalytic subunit of the serine/threonine-protein phosphatase 2A (PP2A) has been found to mediate dephosphorylation of c-Myc and, consequently, its proteasomal degradation (Cianfanelli et al., 2015c; Yeh et al., 2004). This Ambra1-mediated inhibition of cell proliferation is under the control of mTORC1, the inhibition of which triggers c-Myc dephosphorylation in a manner that is clearly dependent on Ambra1 (Cianfanelli et al., 2015c). The function of Ambra1 in this pathway has been delineated to its two recently identified PP2A-interaction regions, termed PXP motifs (see poster); mutations in these motifs prevent the binding of Ambra1 to PP2A, and thus its effect on cell proliferation (Cianfanelli et al., 2015c). Accordingly, mutations in the same regions of *AMBRA1* have also been found to be relevant for tumor initiation (Cianfanelli et al., 2015c). Of note, the role of Ambra1 in the regulation of autophagy is independent of mutations in the PXP motifs, supporting the idea that the pro-autophagic and anti-proliferative functions of Ambra1 depend on different protein regions and, therefore might be, at least in some instances, uncoupled. Nonetheless, a functional role for the interaction between Ambra1 and PP2A in autophagy cannot be ruled out and is worthy of future investigations (Cianfanelli et al., 2015b).

### The role of Ambra1 in development

Ambra1 plays a crucial role during the embryogenesis of vertebrates (Fimia et al., 2007; Skobo et al., 2014; Vázquez et al., 2012). Notably, in contrast to other autophagy-related genes that have been shown to be highly conserved in all eukaryotes, Ambra1 is unique to vertebrates because no orthologs have been found in lower eukaryotes (see above).

During embryogenesis, Ambra1 is highly expressed in the central nervous system (CNS), and in particular, in the neuroepithelium at embryonic day (E)8.5, and in the spinal cord, encephalic vesicles, neural retina and dorsal root ganglia at E11.5 (Fimia et al., 2007; Vázquez et al., 2012). *Ambra1*-deficiency in mouse embryos leads to severe neural tube defects that are associated with autophagy impairment, excessive cell proliferation at early stages, which is followed by increased apoptosis and an accumulation of ubiquitylated proteins in the neuroepithelium (Fimia et al., 2007). The final outcome of *Ambra1* deficiency is embryonic lethality around stage E16.5 (Fimia et al., 2007). Based on this evidence, we can conclude that Ambra1 is an essential protein for controlling cell proliferation and cell survival during development of the CNS. In adult life, it has also been observed that Ambra1 protein sustains, together with Beclin-1, the neuronal stem cell pool within the brain sub-ventricular zone (SVZ), where it is highly expressed, and controls the level of immature neurons by promoting the survival of neural precursor cells (Yazdankhah et al., 2014).

It has been demonstrated recently that Ambra1 is also crucial for myogenesis and that its expression is required for the correct development and morphogenesis of skeletal muscle in zebrafish (Skobo et al., 2014). The zebrafish paralog genes *ambra1a* and *ambra1b* are both required for embryogenesis and also larval development. Ablation of *ambra1a* and *ambra1b*, in fact, leads to reduced locomotor activity and to defects in myofibers and myosepta, which can be rescued by co-injection of human *AMBRA1* mRNA. Although knockdown of one of the two paralog genes is sufficient to alter muscle structure, the double knockdown of *ambra1a* and *ambra1b* results in a more severe phenotype, suggesting that the two proteins, besides working in similar molecular processes, also have distinct roles in fish. Accordingly, a severe myopathy that is characterized by a marked reduction and abnormal orientation of myofibers, disorganization of sarcomeres and abnormal mitochondria morphology has been observed in mice embryos that are homozygous for an *Ambra1* gene trap mutation ($Ambra1^{gt/gt}$) (Skobo et al., 2014).

### Ambra1 and pathologies

Since its discovery in 2007, the *AMBRA1* gene has been associated with a number of pathological conditions, mainly relating to the nervous system. For instance, by means of a genome-wide association approach, an association between a genetic variation on human chromosome 11 and schizophrenia has been demonstrated (Rietschel et al., 2012), and genetic variation in a limited region of chromosome 11 that contains the *AMBRA1* gene has been implicated in schizophrenia etiology. Schizophrenia is a severe psychiatric disorder that is characterized by distortion of thought and perception, with genetic factors contributing substantially to the risk of developing the disease. A study that took a genetic approach has demonstrated an association between *AMBRA1* and various aspects of impulsivity (Heinrich et al., 2013). Recently, a comprehensive behavioral analysis of mice that were heterozygous for an *Ambra1* gene trap mutation ($Ambra1^{+/gt}$) has revealed an autism-like phenotype in adult and pup females, including compromised social interactions, a tendency to exhibit stereotypies or repetitive behaviors and impaired cognitive flexibility (Dere et al., 2014). Another interesting pathological phenotype observed in these $Ambra1^{+/gt}$ mice is a dramatically enhanced and prolonged neuropathic pain that occurs following a nerve insult and axonal degeneration (Marinelli et al., 2014). *Ambra1* haploinsufficiency, which mimics the reduced autophagic response in Schwann cells after nerve injury, results in a painful response that is so pronounced and persistent that mice display self-lesioning behaviors against the injured limb (Marinelli et al., 2014). Besides the observed association between the presence of Ambra1 or its polymorphisms and

neural-related pathologies, there is a strict correlation between *Ambra1* expression and the susceptibility to cancer. In fact, it has been demonstrated that *Ambra1*$^{+/gt}$ heterozygous mice are three times more likely than wild-type littermates to be affected by tumors in lungs, liver and kidney, and that *Ambra1*-deficient cells have a pronounced capability to grow when injected into nude mice (Cianfanelli et al., 2015c). Accordingly, missense, nonsense and frame-shift mutations of the *AMBRA1* gene, which are likely to lead to loss of function, have also been associated with cancer in human tissues (Cianfanelli et al., 2015c). This evidence strongly points to the interaction of Ambra1 with PP2A and its subsequent regulation of the rate of cell division (see above) as the underlying mechanism of *Ambra1*-dependent tumorigenesis.

In the context of the cellular stress response, properly functioning autophagic machinery is also crucial for viral infection. Recently, augmented expression levels of Ambra1 have been found in the peripheral blood mononuclear cells (PBMCs) and lymph nodes of nonprogressor human immunodeficiency virus-1 (HIV-1)-infected individuals, where it contributes to maintaining a robust autophagic response. The sustained autophagy in these individuals is most likely to be responsible for the clinical stability that has been observed in the absence of therapy (Nardacci et al., 2014).

## Concluding remarks

During its life time, a cell is regulated by the integrated activities of energy-supplying organelles, macromolecule-producing systems and recycling approaches. As in our daily life, in our cells, power supply and the production and disposal of waste need to be kept in equilibrium, and internal and external stimuli must be responded to quickly. Autophagy ensures the removal of toxic compounds, as well as of damaged or redundant molecules and organelles through lysosomal degradation and recycling, yet it also participates in essential cell-fate decisions that allow a cell to survive, transform or differentiate. In the past few years, Ambra1 has emerged as a scaffold molecule that serves as a platform for autophagy-related complexes and as an early autophagy regulator, linking this process to a number of other cellular activities. Therefore, in addition to mTOR, Ambra1 appears to be an important switch that governs the cell responses and thus represents an obvious candidate to be targeted in a number of human diseases. However, before this can be achieved, obtaining a more comprehensive understanding of this factor with regard to the elucidation of its multifaceted post-translational modifications needs to be at the forefront of future research efforts.

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#### Competing interests

The authors declare no competing or financial interests.

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#### Cell science at a glance

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