Molecular Neurobiology (2019) 56:6716–6724
https://doi.org/10.1007/s12035-019-1557-7

Neurodevelopmental Disorders: Functional Role of Ambra1 in Autism and Schizophrenia

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Received: 17 January 2019 / Accepted: 13 March 2019 / Published online: 26 March 2019

Abstract

The activating molecule in Beclin-1-regulated autophagy (Ambra1) is a highly intrinsically disordered protein best known for its role as a mediator in autophagy, by favoring the formation of autophagosomes. Additional studies have revealed that Ambra1 is able to coordinate cell responses to stress conditions such as starvation, and it actively participates in cell proliferation, cytoskeletal modification, apoptosis, mitochondria removal, and cell cycle downregulation. All these functions highlight the importance of Ambra1 in crucial physiological events, including metabolism, cell death, and cell division. Importantly, Ambra1 is also crucial for proper embryonic development, and its complete absence in knock-out animal models leads to severe brain morphology defects. In line with this, it has recently been implicated in neurodevelopmental disorders affecting humans, particularly autism spectrum disorders and schizophrenia. Here, we discuss the recent links between Ambra1 and neurodevelopment, particularly focusing on its role during the maturation of hippocampal parvalbumin interneurons and its importance for maintaining a proper excitation/inhibition balance in the brain.

Keywords Ambra1 · Autophagy · Autism spectrum disorder · Schizophrenia · Hippocampus · Parvalbumin interneuron · Excitation/inhibition

Introduction

The activating molecule in Beclin1-regulated autophagy (*Ambra1*) is a newly discovered gene, evolutionarily conserved among vertebrates, codifying for a 1300-amino acid protein [1]. Ambra1 is an "Intrinsically Disordered Protein", characterized by the absence of recognizable domains in its protein sequence, except for three WD40 domains. These domains give this protein the ability to interact with peptides, DNA and other proteins, finely regulating the activation or inhibition of its own function (e.g., by being phosphorylated on different residues or by means of ubiquitylation and subsequent degradation) [2–7].

Ambra1 mediates many and diverse cellular functions, ranging from autophagy [1, 6–11], neuroprotection [12], apoptosis [1, 13–17] and cell proliferation [3, 6, 18], to embryogenesis and neuronal development [1, 13, 14, 19] (Fig. 1). These works have analyzed in depth the molecular mechanisms of Ambra1 function and have been extensively described in many excellent reviews [2, 5, 20–22]. Despite this progress, the involvement of Ambra1 in embryogenesis, particularly in neuronal development, is still relatively unknown [1, 13, 19, 23]. In particular, although Fimia and colleagues described in detail the functional deficiency of Ambra1 in knock-out mouse embryos [1], the effects of a partial loss of Ambra1 protein was not examined. However, the fact that recently Ambra1 has been implicated in human neurodevelopment and in neuropsychiatric disorders such as autism spectrum disorders (ASDs) and schizophrenia [24–26] has prompted us to provide here an overview of the recent progress that elucidates the role of Ambra1 in these processes.

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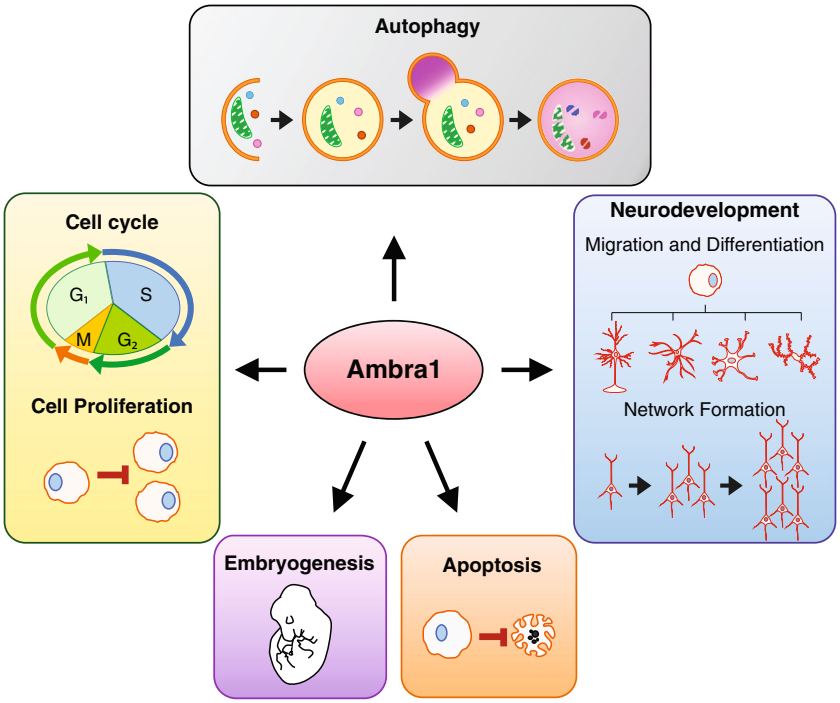

Fig. 1 Role of Ambra1 in different cellular and subcellular processes. Ambra1 is a versatile protein, able to interact with different molecular machines depending on the circumstances a cell finds itself in. One of its most studied roles is autophagy modulation, where it is an important positive regulator during the early stages of autophagosome formation. In addition, it appears to be paramount for cell proliferation, during cell cycle control, and for apoptosis, where it acts as a pro-survival factor. Moreover, Ambra1 plays a pivotal role during embryogenesis, and its downregulation or even a partial loss of function leads to severe nervous system impairments, marking its requirement for a precise and complete neurodevelopment, ranging from neuronal migration, differentiation and maturation, to synaptic network formation

Ambra1 and Neurodevelopmental Disorders

The first evidence linking Ambra1 to neurodevelopmental disorders affecting humans derives from a full battery of behavioral assessment performed in *Ambra1* heterozygous (*Ambra1*$^{+/-}$) mice, from pups to adults [27]. The *Ambra1* haploinsufficient mice displayed a phenotype reminiscent of ASDs that was however restricted to females only [14, 27]. This phenotype was characterized by deficits in social interaction and communication, repetitive behaviors and cognitive rigidity [14, 27]. The gender difference in phenotype appeared to be linked to different levels of the Ambra1 protein, since wild-type females showed a higher basal expression level of Ambra1 than males and thus a much stronger decrease following haploinsufficiency [14, 27]. A similar behavioral study could not be performed in homozygous mice (*Ambra1*$^{-/-}$) as these animals fail to complete normal embryonic development [1], already a strong indication for the involvement of the *Ambra1* gene in embryogenesis. In line with this observation, homozygosity for *Ambra1* deletion causes embryonic lethality at stages E10–E14.5, with defects in neural tube formation detected as midbrain/hindbrain exencephaly and spina bifida, and with reduced numbers of embryonic stem cells in the olfactory bulb [1, 19, 28, 29]. Moreover, detailed analysis of cell death, differentiation and growth in *Ambra1*$^{-/-}$ mouse embryos showed an excessive apoptosis in selected areas of the nervous system and an increase in proliferating neuroepithelium cells, leading to the enlargement of the spinal cord [1]. Analogous data were later obtained from zebrafish [13, 23].

More recently, alterations in Ambra1 protein levels were correlated with ASDs and schizophrenia in humans [24–26]. A phenotype-based genetic association study revealed a correlation between a normal genetic variation of *AMBRA1* (rs3802890-AA/GG) and autistic hallmarks [25]. In particular, the reported intronic single nucleotide polymorphism (SNP) AA was associated with autistic features in female patients, which also display lower *AMBRA1* mRNA expression in peripheral blood mononuclear cells [25]. This evidence suggests a partial loss of function of AMBRA1, correlated with the AA allelic variation. Particularly, the SNP, located within a long non-coding RNA, may affect AMBRA1 stability through modification of folding [25], altering mRNA and protein interaction. Interestingly, similarly to what was observed in *Ambra1*$^{+/-}$ mice [14, 27], no differences were observed in male subjects [25].

In line with AMBRA1's role in neurodevelopment, Rietschel and colleagues observed a strong association between schizophrenia and a genetic risk variation (rs11819869) on chromosome 11, the one containing the *AMBRA1* gene [26]. Additionally, it was demonstrated that an association exists between the risk allele in *AMBRA1*

and delay aversion, a feature of impulsivity [24]. This study reported that risk allele carriers showed a higher medial prefrontal cortex blood oxygen level-dependent (BOLD) response during a flanker task as well as an increase in impulsive aspects, suggesting that the *AMBRA1* risk allele is associated with impulsive-related traits [24]. Interestingly, impulsive behavior is an important feature of several mental illnesses, including schizophrenia, ASDs, bipolar disorder and borderline personality disorder [30–33].

Basis of Neurodevelopmental and Behavioral Dysfunctions Linked to Ambra1

The Importance of the Brain's Excitation/Inhibition Ratio

The central nervous system is organized in a complex network of circuits which require a long gestational period, as well as a fine post-natal maturation, to achieve their full organization [34, 35]. Neurodevelopment occurs in a continuum of neurobiological processes: neurogenesis and neuronal migration are largely prenatal events, and synaptogenesis starts just before birth and is completed during childhood [36]. Meanwhile, synaptic pruning and myelination are not fully achieved until early adulthood [37]. This long stretch of time enables a precise improvement in synaptic connectivity and intracellular dynamics. On the other hand, more time means more vulnerability to environmental insults and an increased probability to develop a genetic dysfunction. Indeed, the increased susceptibility of the brain during development is the basis for most neurodevelopmental disorders in humans, intellectual, or communication disorders ranging from ASDs and attention deficit hyperactivity disorder (ADHD) to neuropsychiatric diseases like schizophrenia and bipolar disorder [30]. All these mental disorders exhibit a wide range of symptoms, including alterations in communication, cognition and behavior, similar to those described for the *Ambra1*$^{+/-}$ female mice [14, 27]. In fact, the implication of AMBRA1 in schizophrenia and ASDs in humans [24–26] might suggest an increased susceptibility of the AMBRA1 gene during development, in line with the fact that Ambra1 is expressed in the brain since the very start of embryogenesis [1].

The noteworthy overlap in signs and symptoms between these various neurodevelopmental disorders, despite an heterologous etiology, has fueled the research for a jointly altered neurobiological system [38]. A point of convergence was proposed at the level of the synapse [39–41]. In fact, synapses are highly specialized structures supporting communication between neurons through a continuous adaptation to neuronal inputs [42, 43] and a balancing of protein synthesis and degradation to maintain homeostasis and support plasticity, the process by which synaptic connections are modified in response to experience and learning [44]. Such a profound structural build-up, with high precision demands, makes this phase more disease-prone. Ambra1's pro-autophagic role is central in driving a precise input onto the autophagic pathway since early embryonic life [1, 5, 7–9, 16, 28], given that at this stage an abundance of proteins needs to be rightly discarded after their biological role has been completed, in a precise time window.

The importance of correct synapse functioning for proper neurodevelopment is highlighted by the fact that a wide range of proteins that are altered in people affected by psychiatric pathologies are fundamental for synaptic transmission [45–47]. The most noteworthy examples are Shank proteins, neurexins and neuroligins, all responsible for scaffolding and adhesion between pre- and postsynaptic terminals [48–54]. In humans, deficits in these proteins have been implicated in schizophrenia and ASD-like symptoms [51, 55–59], while knock-out animal models show discrete brain and behavioral alterations that are consistent with the impairments observed in human patients [60–64].

Interestingly, the studies performed on transgenic animal models reveal that an imbalance between excitatory (mainly glutamatergic) and inhibitory (mainly GABAergic) synaptic transmission is the common culprit in most neurological disorders, including ASDs and schizophrenia [47, 65, 66]. Synaptic dysfunction might affect both excitatory and/or inhibitory synapses, but inhibitory GABAergic interneurons have been pointed out as the main elements that keep brain hyperexcitability under control, the latter being a widespread feature in neurodevelopmental disorders [45, 67, 68]. Today there are many indications, both from humans and rodents, that inhibitory synaptic transmission is impaired (Fig. 2): a brain-wide reduction in GABA receptor subunits [69–74]; a reduction in GAD65 and GAD67, the enzymes responsible for the conversion of glutamate to GABA [14, 75, 76]; an increased ratio of glutamate to GABA [77, 78]; a reduction in parvalbumin (PV) interneurons or PV protein levels, such as in *Shank*$^{-/-}$ and *Shank3b*$^{-/-}$ mice [79] and an increased resting-state activity in the frontal cortex [80, 81], to name a few (reviewed in [45, 47, 65, 82–84]).

Loss of Ambra1 Affects the Development of Hippocampal Parvalbumin Interneurons

When it comes to excitation/inhibition imbalance, one of the most striking attributes of the brain affected by schizophrenia, ASDs or bipolar disorder is the involvement of PV interneurons [45, 65, 77, 85]. These constitute a diverse class of interneurons originating from the medial ganglionic eminence (MGE; [86–88]) and are electrophysiologically identified by their fast-spiking phenotype [82]. PV interneurons constitute ~ 20% of all GABAergic interneurons, thus representing only 2–3% of the total neuronal population in the brain [89]. Nevertheless, due to their fast-spiking nature they can convert

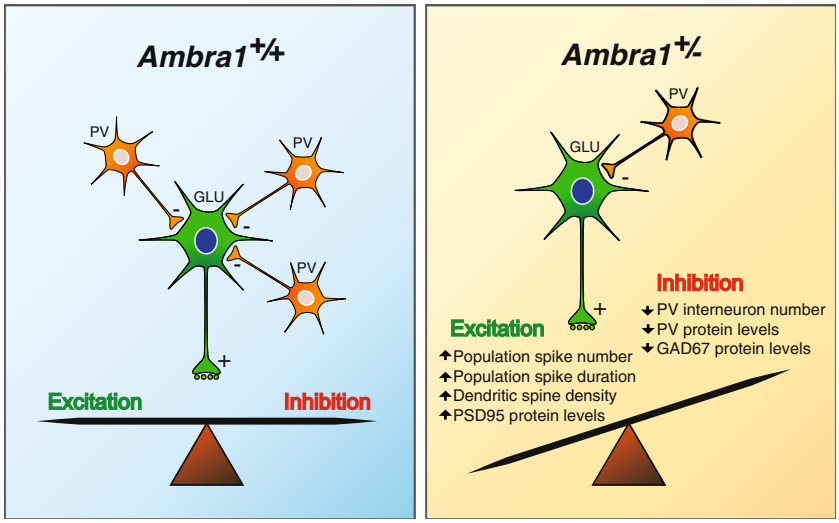

Fig. 2 The crucial role of Ambra1 in the maintenance of the excitation/inhibition balance. In physiological conditions, excitation and inhibition are kept under strict control to ensure a proper excitation/inhibition balance (left panel). In the hippocampus, parvalbumin-expressing (PV) interneurons are the principal inhibitory cells, acting negatively onto excitatory glutamatergic (GLU) pyramidal neurons. Ambra1 heterozygosity in female mice leads to defects in the number of PV interneurons and levels of PV protein and GAD67 (right panel). This brings a lower inhibitory drive onto excitatory neurons, detected as an increase in population spike number and duration, coupled with an increase in dendritic spine density and PSD95 protein levels. All these alterations are typical of an impaired excitation/inhibition balance, leading to behavioral symptoms similar to those observed in female autistic patients

an excitatory input into an inhibitory output signal at the order of milliseconds, providing functional balance, complexity and computational architecture of all neuronal circuits [90]. Indeed, PV interneurons have multiple dendrites that often cross layers, permitting each interneuron to receive inputs from a large population of principal pyramidal cells, while the extensive arborization of their axons can target different subcellular compartments [91, 92]. This allows PV interneurons to play a key role in regulating neuronal excitability via feedback and feed-forward inhibition and in setting the output of principal pyramidal cells, providing the temporal control of the activity of neuronal ensembles, leading to coherent network oscillations [82, 93, 94].

Due to the ability of PV interneurons to control the activity level of principal neurons in the entire brain, if the inhibitory function breaks down excitation takes over, leading to seizures and deficits of higher brain functions. Several events can affect PV interneuron development, number or function, overall leading to excitation/inhibition balance modification [46, 82, 83, 95]. These alterations are particularly associated with changes in gamma oscillations, brain waves mediated by PV interneurons [96–100], that are essential for integration of information in neuronal circuits, such as during memory formation or attention. In fact, changes in gamma oscillations are consistently found in patients with schizophrenia, ADHD, bipolar disorder or ASDs [101–108]. In line with the involvement of PV interneurons in neuropsychiatric diseases, attempts to artificially increase the activity of PV interneurons can restore hippocampal- or prefrontal cortex-related behavioral impairments in mouse models of ASDs and schizophrenia [109, 110].

In this concept, the Ambra1 protein is particularly important for the embryonic development of hippocampal PV interneurons from progenitor cells. In mice, PV interneurons are mainly generated in the MGE between embryonic days E11 and E17, peaking at E13.5 for those neurons destined to migrate to the CA1 region of the hippocampus [86, 87]. Surprisingly, *Ambra1*$^{+/-}$ mouse embryos at E13.5 show increased apoptosis in the MGE, resulting in a pronounced reduction in the number of PV interneurons in the adult hippocampus [14]. Importantly, and in strict compliance with the human and mouse behavioral data linking Ambra1 to neurodevelopmental disorders [14, 24–27], the reduction in PV interneuron number occurs only in female *Ambra1*$^{+/-}$ mice [14]. The authors suggested that this deficit in hippocampal PV interneuron numbers is strictly related to the autism-like phenotype observed in female *Ambra1*$^{+/-}$ mice [14, 27]. Indeed, in agreement with many other studies showing a link between neurodevelopmental disorders, excitation/inhibition imbalance and changes in the population of PV interneurons [45, 82, 83, 95], Nobili et al. showed that female *Ambra1*$^{+/-}$ mice presented a strong imbalance between excitatory and inhibitory synaptic transmission in the hippocampal CA1 [14]. This excitation/inhibition imbalance included reductions in the power of gamma oscillations in vitro (measured by cholinergic receptor activation [111, 112]), reductions in the PV interneuron-mediated inhibition of CA1 pyramidal neurons and brain hyperexcitability [14].

This latter defect in *Ambra1*$^{+/-}$ mice is particularly important since a decrease in inhibitory synaptic transmission can result in a prevalence of excitatory inputs in different areas,

altering circuit homeostasis. Indeed, it was shown that hyperexcitability in the prefrontal cortex reflects onto social behavior, with an impaired social interaction in mice [113, 114]. In the hippocampus, due to a high basal inhibitory activity, even a little decrease in inhibition brings an overabundance of excitatory inputs, resulting in ASD-like behavioral symptoms [115] and pathological manifestations including epilepsy, one of the most common comorbidities affecting people with neurodevelopmental disorders [116–118]. In the case of female *Ambra1*$^{+/-}$ mice, hippocampal hyperexcitability was evident as an increase in the number of pyramidal neuron population spikes—representing an elevated frequency of action potentials—and augmented synaptic plasticity of the Schaffer collateral pathway [14]. The latter appeared to be linked to increased PSD95 levels, the major scaffolding protein in the excitatory postsynaptic compartment [119], and to higher density of synaptic spines in the apical dendrites of *Ambra1*$^{+/-}$ pyramidal neurons [14]. In fact, structural abnormalities or increased numbers of dendritic spines have also been reported in patients and animal models of neurodevelopmental disorders, pointing to incomplete pruning or exaggerated spine formation during neurodevelopment [120–122].

Conclusions

ASDs and schizophrenia are widespread and debilitating neurodevelopmental diseases. Little is known about the cellular and molecular intricacies leading to these pathologies. Even if common manifestations and hallmarks are starting to emerge, bringing different diseases under the same umbrella, there is a desperate need for a treatment directed toward what causes the diseases, rather than having to rely on the symptomatic remedies available today. In this scenario, Ambra1 is a protein directly involved in the molecular pathways thought to be disrupted. Indeed, a wide range of symptoms, including alterations in communication, cognition and behavior, neuronal circuit modifications such as excitation/inhibition imbalance, epilepsy, reduced PV interneuron number and/or functions, and changes in gamma waves, are all features also observed in *Ambra1*$^{+/-}$ female mice. Ambra1's role in forging a healthy interneuron in a healthy neuronal network provides important new clues to what is behind complex diseases, such as ASDs or schizophrenia, and consequently gaining some room for the development of novel treatments.

Many questions are still unanswered, mainly due to the complexity of these pathologies in humans, not yet fully epitomized in any mouse model. Nonetheless, the *Ambra1*$^{+/-}$ mouse has proven to be a valuable tool in basic research. The differential protein expression between females and males after the beginning of gonadal development, coupled with harsher impairments restricted to the female side [14, 27], are interesting in defining what is altered in these pathologies at a microscopical level, also providing a notion for the gender difference observed in humans [25]. Additionally, the *Ambra1*$^{+/-}$ mouse portrays the importance of PV interneurons in maintaining the balance between excitation and inhibition, further advancing the opportunity to intervene in interneuronal function at different stages of neuronal development.

PV neuronal loss occurs during embryogenesis [14], but we cannot exclude that it happens also during migration or postnatal neuronal maturation. Interestingly, during embryonic life PV interneurons display high metabolic demands [123, 124] that require competent mitochondria for constant energy production. Due to the central role of Ambra1 in mitophagy, being pivotal for the elimination of damaged mitochondria [9, 10], its reduction in *Ambra1*$^{+/-}$ mice would be expected to affect most severely the mitophagy process, shifting the balance toward apoptosis. Indeed, among all cellular systems in which Ambra1 indulges, it is likely that autophagy regulation might be the most affected by the haploinsufficiency. This speculation is supported by the fact that autophagic failure, due to dysfunction or loss of other autophagy-related genes (such as *Atg* genes or genes expressing ADNP, Parkin, mTOR or Beclin1), has been strongly associated with neurological dysfunctions and to a variety of neurodegenerative diseases [122, 125–132]. Even beyond autophagy, however, a more in-depth look onto the multifaceted role of Ambra1 in many other key cellular mechanisms is in line with the notion that its partial loss would have multiple impacts on PV cell function, piecing together the puzzle of the pathological phenotype of *Ambra1*$^{+/-}$ mice: it could be likely that an impaired autophagy might exacerbate the effects of a reduced cell proliferation by damaging any survived neurons, or on the other hand, by promoting cell death, so additionally, reducing the number of viable cells. Further studies are needed to decipher why these neurons are particularly sensitive to Ambra1 loss.

To conclude, *Ambra1*$^{+/-}$ mice require further scientific attention in order to disentangle the molecular pathways in the development of ASD-like behavior. A greater understanding of the events that alter PV interneurons and, consequently, excitation and inhibition balance in this model should aid in the development of effective therapies for ASDs, since AMBRA1 has been shown to be involved in humans as well [24–26].

Funding Information A.N. was supported by a post-doctoral Fellowship by the Collegio Ghislieri. P.K. was supported by a post-doctoral Fellowship by the Veronesi Foundation. M.D.A. was supported by an Alzheimer Association's Research Grant (AARG-18-566270).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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