c-Abl kinase at the crossroads of healthy synaptic remodeling and synaptic dysfunction in neurodegenerative diseases

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Abstract
Our ability to learn and remember depends on the active formation, remodeling, and elimination of synapses. Thus, the development and growth of synapses as well as their weakening and elimination are essential for neuronal rewiring. The structural reorganization of synaptic complexes, changes in actin cytoskeleton and organelle dynamics, as well as modulation of gene expression, determine synaptic plasticity. It has been proposed that dysregulation of these key synaptic homeostatic processes underlies the synaptic dysfunction observed in many neurodegenerative diseases. Much is known about downstream signaling of activated N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors; however, other signaling pathways can also contribute to synaptic plasticity and long-lasting changes in learning and memory. The non-receptor tyrosine kinase c-Abl (ABL1) is a key signal transducer of intra and extracellular signals, and it shuttles between the cytoplasm and the nucleus. This review focuses on c-Abl and its synaptic and neuronal functions. Here, we discuss the evidence showing that the activation of c-Abl can be detrimental to neurons, promoting the development of neurodegenerative diseases. Nevertheless, c-Abl activity seems to be in a pivotal balance between healthy synaptic plasticity, regulating dendritic spines remodeling and gene expression after cognitive training, and synaptic dysfunction and loss in neurodegenerative diseases. Thus, c-Abl genetic ablation not only improves learning and memory and modulates the brain genetic program of trained mice, but its absence provides dendritic spines resiliency against damage. Therefore, the present review has been designed to elucidate the common links between c-Abl regulation of structural changes that involve the actin cytoskeleton and organelles dynamics, and the transcriptional program activated during synaptic plasticity. By summarizing the recent discoveries on c-Abl functions, we aim to provide an overview of how its inhibition could be a potentially fruitful treatment to improve degenerative outcomes and delay memory loss.

Key Words: actin cytoskeleton; activity-dependent plasticity; Alzheimer’s disease; c-Abl; dendritic spines; learning; synapse; synaptic plasticity; transcription; tyrosine kinase

Introduction
In the central nervous system, neurons communicate through synapses, highly dynamic structures that, upon stimulation, allow the transmission of information. The synaptic compartment includes actin enriched structures known as dendritic spines, characterized by a pre-synaptic region that contains neurotransmitter vesicles and an electron-dense zone called the post-synaptic density (PSD) that anchors neurotransmitter receptors (Kim et al., 2004). Most hippocampal synapses are glutamatergic in which chemical neurotransmitters are released from vesicles at the pre-synaptic terminal along axons, and received by corresponding N-methyl-D-aspartate receptors (NMDAR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors (AMPAR) at the dendritic post-synaptic compartment. The heads of glutamatergic dendritic spines contain mostly NMDAR and AMPAR, PSD-95 and SAP102 scaffold proteins, cellular organelles, coated vesicles, and cytoskeleton filaments, and polyribosomes for protein synthesis (Sabatini and Svoboda, 2000).

Long-term potentiation (LTP) and long-term depression (LTD) are forms of Hebbian plasticity, the bases of learning and memory that underlie the remodeling of synaptic complexes, changes in the actin cytoskeleton, organelle dynamics, and modulation of gene expression; all processes that can be altered by homeostatic mechanisms (Galánis and Vlachos, 2020). After neuronal stimulation, many kinases and phosphatases orchestrate synaptic plasticity (Woolfrey and Dell’Acqua, 2015). However, there is still much to be learned about the role of phosphorylation modifying mechanisms that control c-Abl activity. It has been proposed that dysregulation of these key synaptic homeostasis processes underlies the synaptic dysfunction characteristic of many neurodevelopmental disorders and neurodegenerative diseases.

In this review, we summarized recent studies showing how c-Abl tyrosine kinase could control homeostatic plasticity through actin cytoskeleton regulation of dendritic spine morphology, and transcription, to alter learning and memory. We will focus on how these different mechanisms could affect neurodegenerative diseases, specifically Alzheimer’s, Parkinson’s, and lysosomal storage diseases.

Activity-Dependent Signaling Entails Synaptic Plasticity
Synapses continuously form and remodel as part of activity-dependent changes in neuronal connections: a process is known as Hebbian synaptic plasticity, which can be altered by homeostatic compensatory mechanisms to restore network functions (Styr and Slutsky, 2018; Galánis and Vlachos, 2020). Hebbian plasticity involves increasing or decreasing the strength of glutamatergic synaptic transmission, mainly known as LTP and LTD respectively, which allows the functional transmission of information, and it is thought to underlie learning and memory (Bin Ibrahim et al., 2022). The early phase of LTP (1–2 hours) depends on AMPAR localization at the PSD; activation of NMDAR subunits GluN2A/B, and the membrane-associated guanylate kinases comprising PSD-95, PSD-93, and SAP102, which are highly

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Review
expressed at excitatory synapses where the receptors are anchored (Chen et al., 2021). During LTP, local protein synthesis is ubiquitous in the post- and pre-synaptic compartments and starts rapidly using mRNAs already located at the synapses (Hofner et al., 2019). Late-LTP (weeks to months) relies on Ca2+-calmodulin proteins (i.e., CaMKII) that couple synaptic activity with the nucleus, promoting the transcription of activity-dependent genes for the de novo protein synthesis required for the generation of memory (Yap and Greenberg, 2018).

LTD involves endocytosis and trafficking of receptors that interchange location, structural reorganization of PSD complexes, and degradation of organelles and synaptic components (Raigor et al., 2021). The elimination of LTD causes deficits in learning and memory through the dysregulation of AMPAR trafficking (Hanley, 2014). The AAA’ AT-Pase Thorase mediates surface internalization of AMPAR by disassembling the AMPAR-GRIK1 complex, therefore affecting glutamatergic transmission. Loss of Thorase enhances LTP and impairs LTD by impeding AMPAR endocytosis (Zhang et al., 2011, Figure 1).

**Figure 1** | Influence of c-Abl on dendritic spines.  
Upper panel: Dendritic spines are synaptic compartments with an electron dense zone, the post-synaptic density (PSD), mostly containing PSD-95 and Shank. N-methyl-D-aspartate receptors (NMDAR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors (AMPAR) are attached to the PSD through PDZ domains. Ephrin A4 receptors respond to Aβ-oligos (AβOs) binding, activating c-Abl to promote neurodegeneration. EphA4, PSD-95 (Y533), F-actin associated proteins Rho/Rac, Rho-associated protein kinase (ROCK), WASP-family verprolin-homologous protein (WAVE) (Y150) and Abl are regulated by c-Abl. Shape changes during maturation are illustrated by confocal microscopy sections of dendritic spines: filopodia (most immature), thin, stubby, mushroom (most mature), branched, or two-headed spines. Bottom panels: c-Abl alters spine density and induces a shift in the morphology of dendritic spines. c-Abl knock-out (c-Abl-KO) mice subjected to cognitive training (MWM: Morris water maze) show increased spine density and display hippocampal neurons that are enriched in mature forms such as mushroom spines (left), AβOs-induced synaptotoxicity decreases spine density independent of c-Abl, and promotes enlargement of spines increasing filopodia, especially in c-Abl-KO neurons. AβOs normally induce apoptosis, but the absence of c-Abl prevents it (right).

Multiple kinases and phosphatases orchestrate synaptic plasticity through the rapid phosphorylation/dephosphorylation of targets that further amplifies signals to the nucleus to promote de novo translation of proteins (Woolfrey and Dell’Acqua, 2015). For example, after neuronal stimulation, CaM kinase II (CaMKII) phosphorylates GluN2B and GluN2A subunits promoting endosomal recycling of the receptor (Yong et al., 2021). CaMKII also phosphorylates the GluA1 subunit of AMPAR, increasing single-channel conductance and synaptic incorporation promoting LTP (Kristensen et al., 2011). Downstream NMDAR, the activation of CaMKII and protein kinase C increases the levels of the AMPAR in the synapse enhancing synaptic strength (Kristensen et al., 2011). Altogether, these functions made CaMKII a promoter of Hebbian plasticity.  

Fyn, a member of the Src family of tyrosine kinases, regulates NMDAR localization and trafficking, stabilizing NR2B-containing NMDARs at the synapse and preventing endocytosis (Salter et al., 2004; Trepnair et al., 2012). On the other hand, STEP phosphatase inactivates Fyn and c-Abl structures and functions. Direct and indirect interactions.  

**c-Abl Structure and Functions**  
c-Abl is a member of the ABL family of tyrosine kinases. The Abelson non-receptor tyrosine kinase (ABL) family includes two members: c-Abl (ABL1), and Arg (ABL-related gene, ABL2) that are ubiquitously expressed in cells. Both share SH2 and SH3 domains, Pro-rich motifs, and F-actin binding domains (BD). Only c-Abl has nuclear localization and nuclear export signals; and a DNA-binding domain that allows nuclear functions related to the regulation of gene expression, DNA damage response, and apoptosis signaling, among others (Coilcelli et al., 2010). In contrast, Arg has a microtubule-binding domain (MT-BD) (Figure 2 upper panel). Therefore, both kinases promote changes in cytoskeleton dynamics through direct and indirect interactions.  

AABL is actively regulated by intracellular and intercellular interactions that allow it to form active or auto-inhibited states (Figure 2 bottom panel). The auto-inhibited conformation of ABL requires the interaction between the SH3 domain and the linker sequence that connects the SH2 and kinase domains (SH1), leading to the formation of a non-covalent dimer (Kemp et al., 2004). The auto-inhibited conformation of ABL shifts the kinase activity to the basal level preventing activation (Figure 2 bottom panel). Specific phosphorylation of c-Abl Y245 in the linker region between the SH2 and kinase domains prevents reversion to the inactive conformation. Phosphorylation on Y412 in the activation loop of the c-Abl kinase domain promotes the catalytic site for substrate phosphorylation (Dorey et al., 2001; Wang et al., 2018). Orthosteric inhibitors such as imatinib and nilotinib compete with ATP preventing phosphorylation (Figure 2 bottom panel). Thus, both Thr phosphorylations promote c-Abl activity.

AABL kinases are key transducers of signals from DNA damage and oxidative stress to activating transcription factors and as growth factors and axon guidance receptors, among other signals. Their substrates are functionally diverse, including adaptors, other kinases, cytoskeletal proteins, transcription factors, chromatin modifiers, and others. Orthosteric ABL1 inhibitors are ubiquitously expressed in neurons, in particular within post- and pre-synaptic terminals, and their activity regulates the reorganization of the cytoskeleton associated with dendrogenesis (Jones et al., 2004; Shaw et al., 2021). Most studies on ABL kinases in the neuronal synapse evaluate the effect of ABL on the SH2 and SH3 domains that locks and regulates its kinase activity. For example, integrin-regulated Arg kinase coordinates the maturation of pre- and post-synaptic compartments by allowing low-release probability GluN2B synapses to replace high-release probability GluN2A synapses during development. This turnover is critical for synaptic plasticity (Xiao et al., 2016). Also, Arg regulates activity-dependent disruption of cortactin localization to stabilize spines and attenuates Rho activity to stabilize dendrite arbors (Lin et al., 2013). There are a few studies about the role of c-Abl in synaptic structure since c-Abl...
has been mostly associated with neurodegenerative diseases because of its participation in altered regulation of cytoskeletal dynamics, gene expression, and apoptosis (Vargas et al., 2018). As we describe here, compelling evidence places c-Abl as one of the main regulators of the most important molecular pathways that regulate the synapse and neuronal homeostasis during synaptic plasticity.

**c-Abl signaling and neuronal cytoskeleton dynamics**

One of the main biological functions of ABL tyrosine kinases is to control actin cytoskeleton remodeling. F-actin is required for the proper development and organization of pre- and post-synaptic components and the formation of cellular structures such as lamellipodial protrusions, filopodia, and dorsal membrane ruffles. c-Abl regulates these processes, which are fundamental for neurite formation and branching, synaptogenesis, and synaptic plasticity (Woodring et al., 2003; Zhang et al., 2018; Gonzalez-Martín et al., 2021).

Multiple experiments using primary cultures of hippocampal neurons have shown that c-Abl modulates neuronal morphogenesis, dendrite outgrowth, and branching. It is also known that c-Abl induces neurite extension by modulating actin cytoskeleton dynamics, either directly through its F-actin binding domain (MT-BD) or indirectly through phosphorylation of actin-binding proteins such as the small GTPase RhoA (Woodring et al., 2003; Jones et al., 2004), and Cdk5 (Zukerberg et al., 2000; Cancino et al., 2011). c-Abl also regulates the Actr2 gene and Arp2 protein, which controls dendritic spine dynamics (Bradley and Koleske, 2003), further suggesting that c-Abl modulates short-term synaptic plasticity.

**c-Abl-dependent transcription**

**Figure 1**

**c-Abl structure and enzymatic regulation.**

Upper panel: Abelson protein tyrosine kinase (ABL) family protein structure: Both, c-Abl and Arg, have an N-terminal kinase domain that starts with a “cap” region, where a phosphorylation can be attached from the high copies of the SH2–SH3 (homologues to Src-family kinases) and an allosteric pocket. At the C-terminal domain, ABL kinases contain proline-rich sequences (PxxP) that mediate protein-protein interactions due to affinity to SH3-containing proteins and filamentous (F-)actin binding domains (F-actin binding domain) that contain a globular (G-)actin binding domain (GBD) in contrast to Arg, which contains two F-actin and a microtubule-binding domain (MT-BD). Another key difference is that only c-Abl has DNA binding domain (DNA-BD) sequences, nuclear export signals (NES), and nuclear localization signals (NLS). Bottom panel: SH2 domain binds into the allosteric site of the C-Sob, the myristoyl pocket, and generates an autoinhibited conformation, enhanced by allosteric inhibitors GNF-2 and GNF-5. Release of the SH2-SH3 domain by phosphorylation of Y245 and Y412 of the SH2-SH3 domain promotes the auto-inhibition. Orthothoracic inhibitors imatinib, ponatinib, nilotinib, and dasatinib bind to the activation loop.

PSD-95 undergoes post-translational modifications, including palmitoylation and serine/threonine phosphorylation that regulates its attachment to NMDAR (Kim et al., 2007). Our group also described that c-Abl co-localizes with PSD-95 and controls through Tyr phosphorylation the activation of PSD-95 on Y533 (Figure 1). Inhibition of c-Abl with imatinib and transient genetic ablation of the c-Abl kinase domain (c-Abl-KD) decreases the area of PSD-95 clusters and PSD-95/Synapsin synaptic contacts without variation in the number of dendritic spines (de Arce et al., 2018). However, if c-Abl knockdown (KO) cultured neurons, the number of PSD-95 clusters was similar to wild-type neurons (Gutierrez et al., 2019), further suggesting that compensatory mechanisms are taking place to ensure synaptic structure. On the other hand, c-Abl blocks Rac1 and Arp2/3 and N-WASP in dendritic spines (Piccolo et al., 2021). Thus, c-Abl has been significantly enhanced in the absence of c-Abl, while synaptic contacts PSD-95/Piccolo did not vary. Therefore, c-Abl could be differentially influencing pre-synaptic proteins. Since Piccolo is a scaffold protein of the active zone at the presynaptic terminal that maintains the clustering of synaptic vesicles (Gundelfinger et al., 2016), it could be affected by c-Abl regulation of the actin cytoskeleton, which is crucial for vesicle mobilization, trafficking, and neurotransmitter release. However, it has also been shown that c-Abl regulates neurotransmitter release from Schaffer collateral-CA1 synapses (Moresco et al., 2003). Electrophysiological studies showed that c-Abl modulates the efficiency of neurotransmitter release from the pre-synaptic terminal, and c-Abl-KO mice had reduced pulse paired-facilitation (Moresco and Kosake, 2003), further suggesting that c-Abl modulates short-term synaptic plasticity.

**c-Abl and synaptic complexes**

Figure 2

In the brain, c-Abl is highly conserved, and its activity is required for brain function and behavior. For instance, c-Abl is necessary for normal learning and memory processes, and its inhibition leads to impaired memory formation in the fear-conditioning memory task (Zuñiga et al., 2014; Amador and Koleske, 2018). Therefore, these results suggest that c-Abl participates in synaptic cytoskeletal remodeling during learning. After hippocampal-dependent tasks, c-Abl-KO mice overexpress wild-type mice performance and, accordingly, show an enriched spine population with increased head size (Gonzalez-Martín et al., 2021). The bigger spine head size also increases the contact area with pre-synaptic axonal terminals, and the number of neurotransmitter receptors for a new stimulus, strengthening the synapse. Furthermore, c-Abl regulates neurotransmitter release at Schaffer collateral-CA1 synapses (de Arce et al., 2018), further suggesting that c-Abl modulates short-term synaptic plasticity.

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Review

Alzheimer’s disease

Alzheimer’s disease (AD) is the main form of dementia in people over 60 years. It affects the brain centers of learning and memory: the entorhinal cortex, and the hippocampus (Viola and Klein, 2015). AD is a neurodegenerative disease characterized by histopathological hallmarks that include the accumulation of senile plaques consisting of aberrant extracellular aggregates of the amyloid-beta (Aβ) peptide and intracellular extracellular plaques and neurofibrillary tangles.

Figure 3 | c-Abl implications in neurodegenerative diseases focusing on Alzheimer’s disease (AD), Parkinson’s disease (PD), and lysosomal storage diseases (LSDs).

Summary of cytoplasmic and nuclear functions of c-Abl in neurodegenerative diseases compared with the basal healthy condition. In healthy neurons, different rates of c-Abl kinase activity control the actin cytoskeleton to remodel the synapse. However, it also acts as a brake for transcriptional regulation of cytoskeletal genes like Arp2/3, and synaptic genes like Atad1, which controls AMPARs recycling. c-Abl phosphorylates RNA polymerase II (RNAPII) (Y1) to terminate transcription. In AD, Aβ-oligomers (AβOs) induce the activation of the Ephrin A4 (EphA4) receptor that activates c-Abl (Y412) to control actin cytoskeleton remodeling and dendritic spine loss. Active c-Abl controls Tau hyperphosphorylation (Y197, Y212, Y233) and recruits to promoters of synaptic genes, favoring transcription. In PD, alpha-synuclein (α-syn) aggregates induce aberrant c-Abl activation that phosphorylates synuclein (Y39) and inactivates parkin (Y143), promoting oxidative stress and dysregulation of mitochondrial biogenesis and autophagy. In the LSD Niemann Pick C (NPC) disease, cholesterol accumulation into the lysosomes induces aberrant c-Abl activation that phosphorylates transcription factor EB (TFEB) (Y173), blocks its translocation into the nucleus, and downregulates gene expression. In Gaucher disease (GD), glucosylceramide accumulation into the lysosomes induces aberrant c-Abl activation that phosphorylates transcription factor EB (TFEB) (Y173), blocks its translocation into the nucleus, and downregulates gene expression. In Gaucher disease (GD), glucosylceramide accumulation into the lysosomes induces aberrant c-Abl activation that phosphorylates transcription factor EB (TFEB) (Y173), blocks its translocation into the nucleus, and downregulates gene expression. In Gaucher disease (GD), glucosylceramide accumulation into the lysosomes induces aberrant c-Abl activation that phosphorylates transcription factor EB (TFEB) (Y173), blocks its translocation into the nucleus, and downregulates gene expression.

Moreover, c-Abl phosphorylates the CTD-Tyr1 of RNA Polymerase II (RNAPII) during transcription-coupled DNA double-strand breaks (DSBs) in proliferating cells (Burger et al., 2019). Others suggest that RNAPII is poised at activity-induced genes in neurons to rapidly promote transcription through DSBs (Madabhushi et al., 2015), but less is known about RNAPII/c-Abl in neurons.

Altogether, these studies indicate that c-Abl affects the synapse, either directly through the actin-cytoskeleton and receptor trafficking, or as a transcriptional regulator of the proteins involved. Therefore, it is a part of the mechanism of homeostatic plasticity. However, due to the various functions that c-Abl fulfills in the cell, understanding how its differential localization and kinase activity rates contribute to dendritic spine remodeling is difficult to understand completely.
deposits of hyperphosphorylated tau protein known as neurofibrillary tangles (NFTs) (Hardy and Higgins, 1992; Alonso et al., 2018). C-Abl is activated in AD patients’ brains, and in vitro and in vivo AD models (Alvarez et al., 2004; Jing et al., 2009; Olabarria et al., 2019), suggesting a potential role for C-Abl in AD neurodegeneration.

Synaptopathogenesis characterizes early AD where Aβ-oligomers (AβOs) bind to the synapse and ultimately promote neuronal death (Fiala et al., 2002; Sciacca et al., 2021). The morphological changes that decrease the strength of the synapse usually found include abnormal filopodial shapes, reduced number, enhanced ectopic spine formation, and shrinkage of dendritic spines (Maiti et al., 2015). Due to Aβ synaptic toxic properties, it has been proposed as a blocker of Hebbian plasticity and promotion of homeostatic synaptic plasticity. However, because of neuronal firing alterations and Aβ-phosphorylation, mechanisms by which cholesterol modulates synaptic plasticity are not clear in early AD (Styr and Slutsky, 2018; Galanis and Vlachos, 2020).

Our studies showed that the EphA4 receptor binds AβOs; phosphorylates, and causes downstream activation of c-Abl, inducing synaptic loss and LTP blockade. The EphA4 receptor antagonist peptide KLY or imatinib treatment prevents dendritic spine density loss and improves neuronal survival (Vargas et al., 2014). Showing that the Ephrin/C-Cbl axis is a key signaling pathway in early AD (Figure 3) (for further information, see Vargas et al., 2018). In vitro models for early-AD have shown that c-Abl absence causes the enlargement of the dendritic spine head and increased spine density, as well as maintaining dendritic spine density and promoting the lengthening of the spines while the mushroom population remains (Gutierrez et al., 2019; Figure 1 bottom panel right). Therefore, a transient spine population predominates after AβOs exposure in the absence of c-Abl.

Downstream activation of c-Abl with AβOs triggers the phosphorylation and degradation of the mammalian target of rapamycin (mTOR) activator gene GAPDH1/ubiquitin-protein ligase (Ube3A)3 (Lauretti et al., 2020). The gap junctions and the degradation of Arc and Ephexin-5. When these proteins accumulate, surface AMPAR-GluR1 subunit and spine density decrease. Accordingly, c-Abl inhibition overrides this effect (Olabarria et al., 2019). Thus, the resilience against AβOs damage in the absence of c-Abl can be explained by the c-Abl regulation of the actin cytoskeleton/Arc/3p, and Ube3A/Arc/Ephexin-5.

C-Abl has nuclear functions that could worsen AD pathology. During long incubation with AβOs, C-Abl kinase activity prompts p73 phosphorylation and the expression of apoptotic genes that trigger neuronal apoptosis (Cancino et al., 2008; Wetzel et al., 2008). Interestingly, the chemically induced c-Abl kinase activity in vitro promotes and decreased HDAC2 reductions in neuronal promoters (González-Zuñiga et al., 2014; Figure 3). Therefore, c-Abl promotes HDAC2 transcriptional repression activity and worsens AD neuropathology.

Moreover, c-Abl activity has been linked to alterations in tau protein, a classic pathological change in AD. ABL kinases directly phosphorylate tau on Y197, Y210, and Y394; however, only Y197/Y394 is phosphorylated in the NFTs in AD (Tremblay et al., 2010). C-Abl regulates downstream substrates that collectively contribute to tau phosphorylation and NFT formation in AD. For example, Cdk5 activity is elevated in the AD brain, and when deregulated, it contributes to the phosphorylation of p42/p44 MAPK, which plays a role in the degradation of Arc and Ephexin-5. When these proteins accumulate, surface AMPAR-GluR1 subunit and spine density decrease. Accordingly, c-Abl inhibition overrides this effect (Olabarria et al., 2019). Thus, the resilience against AβOs damage in the absence of c-Abl can be explained by the c-Abl regulation of the actin cytoskeleton/Arc/3p, and Ube3A/Arc/Ephexin-5.

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activated c-Abl emerges as a common link to several PD-related inducers of oxidative stress relevant to sporadic and familial forms of PD and other α-synucleinopathies (Brahmachari et al., 2016). c-Abl directly phosphorylates α-synuclein in Tyr39 inducing its aggregation. C-Abl inhibition with nilotinib promotes α-synuclein clearance via the autophagy and proteasome pathways (Mahul-Mellier et al., 2014). α-Synuclein inclusions cause a major reduction in neuronal connectivity, synchronicity, and excitatory tone (Volpicelli-Daley et al., 2004). These aggregates can disrupt LTP in striatal spines and neurons, and induce a reduction in surface levels of GluN2A-NMDAR, leading to decreased NMDAR currents. Therefore, aberrant c-Abl activation that promotes α-synuclein aggregation, could play a role in targeting NMDA/AMPA receptors to the cell surface, directly affecting synaptic transmission and plasticity in PD.

In the MPTP mouse model of PD, nilotinib ameliorates motor deficits by normalizing altered activity in postsynaptic signaling pathways in the striatum. Specifically, prevents the increase of phosphorylated Cdks-Tyr15 and DARPP-32-Thr75 mediated by c-Abl (Tanabe et al., 2014), supporting the protective potential of c-Abl in synaptic plasticity defects (Figure 3). Also, the C-Abl-Grx2 pathway mediates autophagy by inhibiting TFEB nuclear localization with the subsequent neuronal loss in primary midbrain neurons treated with MMP (Ren et al., 2018).

Overexpression of the constitutively active form of c-Abl (CA) accelerates neurodegeneration through the accumulation of ubiquitinated proteins, which exacerbates behavioral deficits and reduces the lifespan of hA53T α-synuclein transgenic mice (Brahmachari et al., 2016). Moreover, C-Abl-CA overexpression is sufficient for the degeneration of dopaminergic neurons in 19 months of wild-type mice. In contrast, C-Abl-XO increases the survival of hA53T mice and delays behavioral, neurodegenerative, and pathological features (Brahmachari et al., 2016).

C-Abl also phosphorylates parkin in Tyr143, which leads to the disruption of its E3-ligase enzymatic activity and the impairment of parkin-dependent pathways for protein clearance of phosphorylated/internalized α-synuclein aggregates or plaques (Ko et al., 2010). This C-Abl-GSK3 pathway mediates autophagy by inhibiting TFEB nuclear localization with the subsequent neuronal loss in primary midbrain neurons treated with MMP (Ren et al., 2018).

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**Summary**

In this review, we mentioned different functions of the non-receptor tyrosine kinase c-Abl (ABL1) to elucidate how its activation in the brain affects learning and memory. We reviewed Abl kinase structure to highlight the differences between Abl and c-Abl on its actin and DNA-binding domains, and nuclear localization signals that allow c-Abl to respond to a wide variety of stimuli. We embarked on our task into Hebbian and homeostatic synaptic plasticity by reviewing different molecular pathways that participate in altering the morphology of dendritic spines. These structures attract the special attention of scientists for being the center of learning and memory, as first described by Santiago Ramón y Cajal. Alterations of dendritic spines' shape, size, and density, are usually found in neurodegenerative diseases. However, not every change in the shape and number of the dendritic spines is detrimental, as they also occur during synaptic plasticity. In this context, in absence of c-Abl, the dendritic spine's head width and number number increases in response to activity-dependent plasticity or LTP after conditioned learning, as we hypothesized, acting as a promoter of Hebbian synaptic plasticity. However, c-Abl overactivation contributes to worsening the outcome of neurodegenerative diseases, acting as a homeostatic mechanism of synaptic plasticity.

Finally, we analyzed c-Abl involvement in AD, PD, and LSD to emphasize that pharmacological inhibition of c-Abl with small and central nervous system permeable inhibitors could be a valuable strategy for treating the cognitive decline and memory impairments characteristic of these diseases. Therefore, we reviewed different molecular pathways that contribute in altering the morphology of dendritic spines. These structures attract the special attention of scientists for being the center of learning and memory, as first described by Santiago Ramón y Cajal. Alterations of dendritic spines' shape, size, and density, are usually found in neurodegenerative diseases. However, not every change in the shape and number of the dendritic spines is detrimental, as they also occur during synaptic plasticity. In this context, in absence of c-Abl, the dendritic spine's head width and number number increases in response to activity-dependent plasticity or LTP after conditioned learning, as we hypothesized, acting as a promoter of Hebbian synaptic plasticity. However, c-Abl overactivation contributes to worsening the outcome of neurodegenerative diseases, acting as a homeostatic mechanism of synaptic plasticity.

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