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Pin1 in Neuronal Apoptosis

Esther B.E. Becker and **Azad Bonni***
Department of Pathology; Harvard Medical School; Boston, Massachusetts USA

Abstract

While the role of the prolyl isomerase Pin1 in dividing cells has long been recognized, Pin1's function in postmitotic neurons is poorly understood. We have identified a novel mechanism by which Pin1 mediates activation of the mitochondrial cell death machinery specifically in neurons. This perspective presents a sophisticated signaling pathway that triggers neuronal apoptosis upon JNK-mediated phosphorylation of the BH3-only protein BIM_{EL} at serine 65. Pin1 is enriched at the mitochondria in neurons together with BIM_{EL} and components of a neuron-specific JNK signaling complex and functions as a molecular switch that couples the phosphorylation of BIM_{EL} by JNK to apoptosis specifically in neurons. We discuss how these findings relate to our understanding of the development of the nervous system and the pathogenesis of neurologic disorders.

Keywords

cell death; neuron; Pin1; BIM; JNK

The PROLYL ISOMERASE PIN1

In recent years, phosphorylation-dependent prolyl isomerization has emerged as a major post-translational signaling mechanism. A growing number of phosphorylated proteins participating in important cellular processes are regulated through prolyl isomerization-induced conformational changes. The cis-trans configuration of peptide bonds between (phosphorylated) serine or threonine residues and an adjacent proline residue can have significant effects on protein phosphorylation status, as well as protein structure, activity, and stability and therefore needs to be carefully controlled by the cell.

The isomerization of phosphorylated serine/threonine-proline motifs is efficiently catalyzed by the prolyl isomerase Pin1.[1] Pin1 contains an amino-terminal WW domain that specifically interacts with phosphorylated serine/threonine motifs and a carboxyl-terminal enzymatic peptidyl prolyl isomerase domain. Pin1-interacting motifs in substrate proteins are generated by proline-dependent kinases, which are pivotal players in numerous cellular signaling pathways.[2] Pin1 was originally identified as an interacting protein of the fungal mitotic kinase NIMA, pointing to an essential role for Pin1 in mitosis.[3] Subsequently, numerous studies have established a role for Pin1 in cell cycle progression and proliferation. Pin1 regulates the progression of the cell cycle by interacting with a large number of mitotic phosphoproteins including Cdc25 and cyclin D as well as transcription factors such as beta-catenin.[4,5] Many mitotic substrates of Pin1 are phosphorylated by the kinase Cdc2 (also known as cyclin-dependent kinase 1 {Cdk1}), a master regulator of mitosis. Interestingly, misregulation of both Cdc2 and Pin1 in dividing cells can lead to blocked mitosis and mitotic catastrophe,[3,6,7]

*Correspondence to: Azad Bonni; Department of Pathology; Harvard Medical, School; 77 Avenue Louis Pasteur; Boston, Massachusetts 02115 USA; Tel.: 617.432.4104; Fax: 617.432.4101; Email: azad_bonni@hms.harvard.edu.

suggesting that both proteins function in the same mitotic pathways. Consistent with its role in cellular proliferation, Pin1 is overexpressed in many common types of cancer including prostate, breast, lung, and colon cancer.[8] Furthermore, increased Pin1 expression correlates with poor prognosis of these tumors.[8–10]

Surprisingly, Pin1 levels are high in neurons, which are terminally differentiated and postmitotic cells,[11,12] suggesting additional functions for Pin1 in neurons distinct from cell cycle regulation and proliferation. Pin1 has been proposed to play a role in age-dependent neurodegeneration associated with hyperphosphorylated tau.[13] We have recently identified a novel neural-specific mechanism of apoptosis, whereby Pin1 activates the mitochondrial cell death machinery in neurons following trophic factor and activity deprivation.[11]

APOPTOSIS IN THE NERVOUS SYSTEM

Apoptosis of neurons is a conserved and fundamental process in the development of the nervous system. The nervous system is initially generated with an excess number of neurons, followed by extensive apoptosis that ensures the proper assembly of neural circuits.[14,15] In the adult brain, neuronal apoptosis contributes to the pathogenesis of several common neurologic disorders including ischemia and hereditary motor neuron diseases.[16–18] Given the importance of neuronal cell death in brain development and disease, the molecular underpinnings of neuronal cell death are the subject of intense scrutiny. It has become apparent that the mitochondrial apoptotic machinery plays an essential role in the control of neuronal cell death.[19] Ultimately, almost all survival and death signaling pathways in neurons converge at the mitochondria where they are integrated mainly by the BCL-2 family of proteins.[20] In particular, members of the pro-apoptotic BH3-only subfamily are critical for the activation of the mitochondrial cell death program by acting as upstream sentinels of cellular damage that transduce apoptotic signals to the mitochondrial cell death machinery.[21]

The mitochondrial BH3-only protein BIM_{EL} is a key regulator of neuronal apoptosis following trophic factor deprivation as well as activation of the p75 cell death receptor ($p75^{NTR}$).[22–24] In addition to its contribution to developmental neuronal cell death, BIM_{EL} has been implicated in Alzheimer's disease and ischemia.[25–27] The apoptotic function of BIM_{EL} in neurons is controlled at several levels including transcriptional and post-translational mechanisms. One of the key regulators of BIM_{EL} in neurons is the c-Jun N-terminal kinase (JNK) signaling pathway, which is one of the major signaling pathways activated by numerous apoptotic stimuli in neurons including growth factor withdrawal and excitotoxicity.[28–30] In addition to upregulating *bim* gene expression through the activation of the transcription factor c-Jun,[23,24,31] JNK also directly phosphorylates the BIM_{EL} protein at the distinct site of serine 65.[22,32] Phosphorylation of BIM_{EL} at serine 65 activates the apoptotic function of BIM_{EL} in neurons. Intriguingly, phosphorylation of BIM_{EL} at the same site in proliferating non-neural cells suppresses cell death, possibly through the proteasomal degradation of phosphorylated BIM_{EL}.[33–35] The critical regulatory phosphorylation event of BIM_{EL} at serine 65 provides therefore a foundation for the elucidation of neural-specific cell death activation. We have proposed a Pin1-dependent mechanism by which phosphorylation of BIM_{EL} at serine 65 leads to the activation of the mitochondrial apoptotic machinery specifically in neurons.[11] Our findings and their implications for neuronal function are discussed below.

PIN1 IS AN IMPORTANT MEDIATOR OF NEURONAL APOPTOSIS

Our studies shed light on the important question of how apoptosis is regulated in a cell-specific manner in the nervous system. We showed that Pin1 interacts specifically with serine 65-phosphorylated BIM_{EL} and thereby stabilizes BIM_{EL}, resulting in neuronal apoptosis. These findings are the first to implicate Pin1 in the direct regulation of the mitochondrial cell death machinery. Pin1 might be posited to promote apoptosis by simply binding to serine 65-

phosphorylated BIM_{EL} via its WW domain and thereby protecting BIM_{EL} from degradation. However, we demonstrated that the isomerase activity of Pin1 is also required for Pin1's function in neuronal apoptosis. These findings suggest that BIM_{EL} undergoes isomerization following phosphorylation of serine 65, resulting in increased resistance of BIM_{EL} to proteasomal degradation and hence increased stabilization of BIM_{EL}. The underlying mechanism for this stabilization of BIM_{EL} remains to be identified. Pin1-mediated isomerization of serine 65-phosphorylated BIM_{EL} might change the cis-trans configuration of the BIM_{EL} phosphodegron motif that is recognized by an undefined E3 ubiquitin ligase, thereby reducing its affinity for BIM_{EL}. A link between Pin1-mediated isomerization and ubiquitination, although promoting degradation, has recently been reported for the Pin1 substrate cyclin E.[36] It will be important in the future to characterize the mechanism of phosphorylation-dependent degradation of BIM_{EL} in greater detail. While some studies reported proteasomal degradation of BIM_{EL} following phosphorylation at serine 65,[33,34] others did not observe clearance of serine 65-phosphorylated BIM_{EL}.[35,37] Importantly, to date no ubiquitin ligase has been identified that binds to serine 65-phosphorylated BIM_{EL} in neurons.

In addition to interfering with the recognition by ubiquitin ligases, Pin1-mediated isomerization could result in a conformational change in serine 65-phosphorylated BIM_{EL} that might lead to the activation of BIM_{EL}. An attractive hypothesis is that the motif containing serine 65 might act as an (auto)inhibitory domain that regulates the apoptotic function of BIM_{EL}. A similar mechanism has been reported for two other BCL-2 family proteins, namely BCL-2 and BCL-X_L, which are both regulated by post-translational modifications including JNK-mediated phosphorylation.[38–40] To investigate the effect of Pin1-mediated isomerization on the conformation of BIM_{EL}, it will be imperative to perform structural studies on BIM_{EL} alone and serine 65-phosphorylated BIM_{EL} in complex with Pin1.

Our findings raised the intriguing question of how Pin1, a protein strongly expressed in proliferating cells as well as in neurons, could be the molecular switch determining the cell type-specific consequences of BIM_{EL} phosphorylation at serine 65. We reasoned that Pin1's function in the activation of the mitochondrial apoptotic machinery in neurons might be conferred by a distinct subcellular localization of Pin1 in neurons. In non-neural cells, Pin1 has been reported to primarily localize to the nucleus.[7] Interestingly, we found that a significant proportion of Pin1 in neural but not in non-neural cells is tethered to the mitochondrial membrane. This allows Pin1 specifically in neurons to be in close proximity with its substrate BIM_{EL}, which is also localized to the mitochondria. In contrast, in non-neural cells Pin1 and BIM_{EL} are localized to different cellular compartments, which might allow for the prompt degradation of BIM_{EL} following phosphorylation at serine 65.

What allows for the distinctive localization of Pin1 to the mitochondria in neurons? The selective enrichment of Pin1 at the mitochondrial membrane in neurons may be achieved through Pin1's interaction with a neuron-specific JNK signaling complex.[11] JNK signaling proteins are organized by scaffold proteins that coordinate activation and specificity of signal transduction.[41] The JNK-interacting protein 3 (JIP3) is a neuron-enriched JNK scaffold protein,[42,43] and significant amounts of JIP3 and other components of the JNK signaling pathway are localized at the mitochondrial membrane in neurons.[11,32] Interestingly, we found that Pin1 is associated with JIP3 in neurons in a phosphorylation-dependent manner. Our findings suggest a central role for the JIP3 signaling complex in neuronal apoptosis by providing both the kinase (JNK) and the post-phosphorylation isomerase activity (Pin1) to BIM_{EL} at the mitochondrial membrane. The organization of both of these enzymatic activities by the JIP3 complex may serve to efficiently activate BIM_{EL} in neurons and offers an explanation for the neuron-specific activation of the mitochondrial apoptotic machinery by the ubiquitously expressed Pin1.

While we have focused on Pin1 as a mediator of BIM_{EL}-induced neuronal apoptosis, Pin1 may have a more general role in neuronal cell death. Given Pin1's intimate link with JIP3 and JNK signaling in neurons, it will be interesting to determine whether Pin1 regulates other substrates of JNK following apoptotic stimuli in neurons.

Remarkably, in addition to the stress-activated protein kinases, the mitotic kinase Cdc2 has emerged as a key mediator of neuronal apoptosis during brain development and disease.[44] Since Cdc2 generates numerous substrates for Pin1 in proliferating cells, Pin1 might also contribute to Cdc2-induced neuronal cell death. One of the apoptotic targets of Cdc2 in neurons is the BH3-only protein BAD.[45] Cdc2 phosphorylates BAD at serine 128, resulting in the inhibition of the interaction of BAD with sequestering 14-3-3 proteins and hence the activation of BAD's apoptotic function in neurons. Interestingly, JNK also phosphorylates BAD at Serine 128 and thereyby activates BAD-mediated apoptosis in neurons.[46] Similar to the phosphorylation of BIM_{EL} at serine 65, phosphorylation of BAD at serine 128 on its own does not trigger apoptosis in proliferating cells.[17,48] In light of our study, it is tempting to speculate that Pin1 acts as a more general molecular switch that couples the phosphorylation of components of the apoptotic machinery to cell death specifically in neurons. In the case of serine 128-phosphorylated BAD, it is conceivable that Pin1-mediated isomerization causes a conformational change in BAD that results in the disruption of BAD's sequestration by 14-3-3 proteins.

The function of cell cycle proteins in neurons is not restricted to apoptosis, as cell cycle proteins have been recently shown to regulate other essential neuronal processes including axonal growth and patterning in the developing brain.[49,50] It will be therefore very interesting to determine whether Pin1 also functions in other cell cycle protein-mediated processes in the nervous system.

Our study raises the attractive possibility that Pin1's specific role in the activation of the mitochondrial apoptotic machinery in neurons might contribute to the pathogenesis of neurologic disorders. Both JNK signaling and cell cycle reactivation have been implicated in neuronal apoptosis under pathologic conditions including ischemia and neurodegeneration.[44,51] The role of Pin1 in neuronal apoptosis in the mature brain remains to be established. Future studies of neurologic disease models in Pin1-deficient and -overexpressing mouse models will give important insights into the contribution of Pin1 to neuronal apoptosis in vivo. The information gained from such studies will be invaluable in determining whether manipulation of Pin1 and its interaction with JIP3 might be a viable strategy for the treatment of human neurologic diseases.

ABBREVIATIONS

BAD, BCL-2 associated death agonist; BCL-2, B-cell leukemia/lymphoma 2; BIM, BCL-2-interacting mediator of cell death; JIP3, JNK-interacting protein 3; JNK, c-Jun N-terminal kinase.

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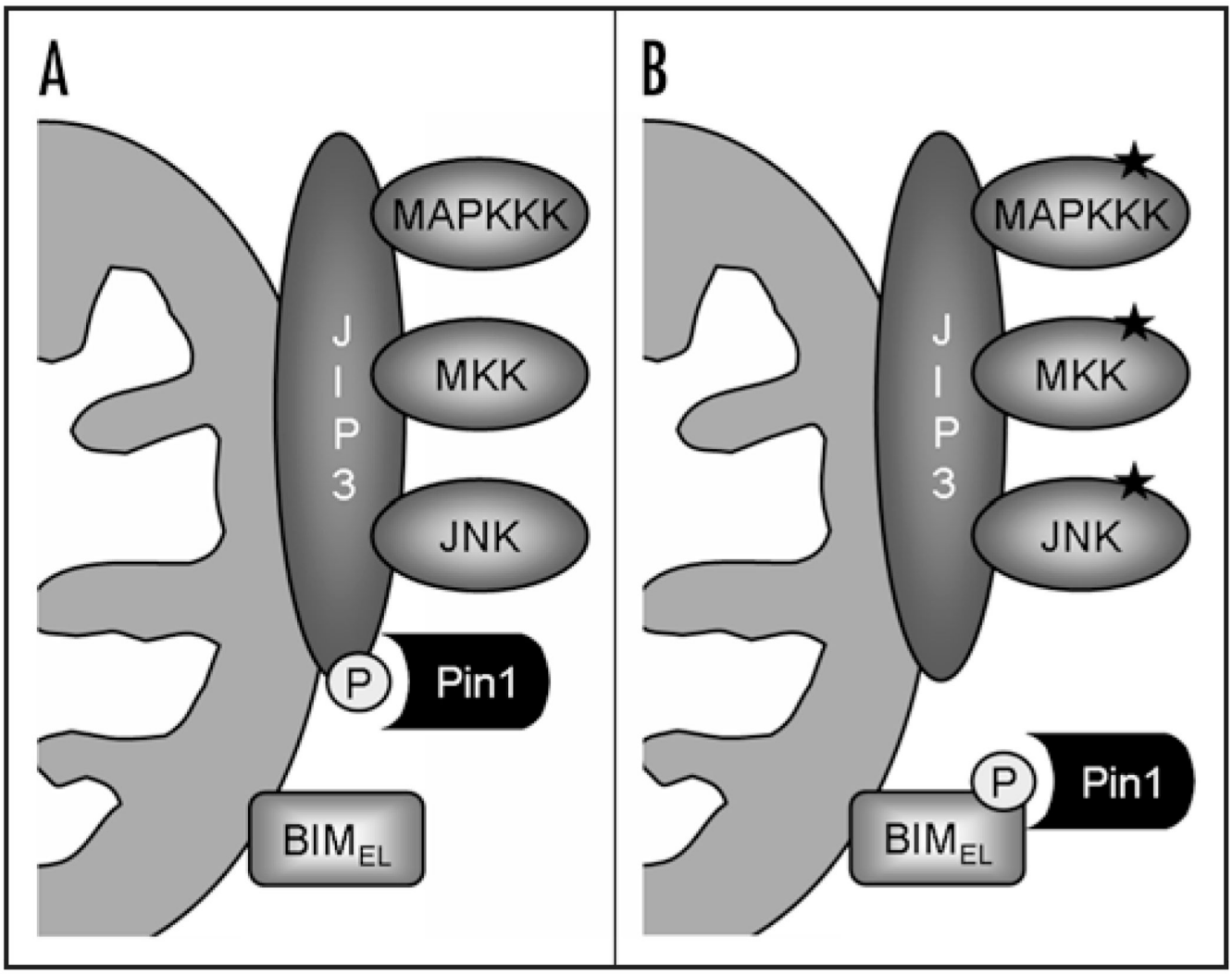

Figure 1.

Model of neural-specific Pin1-mediated activation of BIM_{EL} following JNK-induced phosphorylation of BIM_{EL} at serine 65. (A) In neurons, Pin1 is tethered to the mitochondria through binding to the neuron-enriched JNK-scaffolding protein JIP3, where it is in close proximity to its substrate BIM_{EL}. (B) Upon an apoptotic stimulus, JNK signaling is activated, which results in phosphorylation of BIM_{EL} at serine 65. Pin1 is released from JIP3 and interacts specifically with serine 65-phosphorylated BIM_{EL}, thereby stabilizing BIM_{EL} and activating BIM_{EL}-mediated neuronal apoptosis.