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Review

Pin1 dysregulation helps to explain the inverse association between cancer and Alzheimer's disease☆

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ABSTRACT

Background: Pin1 is an intracellular signaling molecule which plays a critical but opposite role in the pathogenesis of Alzheimer's disease (AD) and many human cancers.
Scope of review: We review the structure and function of the Pin1 enzyme, the diverse roles it plays in cycling cells and neurons, the epidemiologic evidence for the inverse association between cancer and AD, and the potential therapeutic implications of Pin1-based therapies.
Major conclusions: Pin1 is a unique enzyme that has effects on the function of target proteins by "twisting" them into different shapes. Cycling cells use Pin1 to help coordinate cell division. It is over-expressed and/or activated by multiple mechanisms in many common human cancers, and acts on multiple signal pathways to promote tumorigenesis. Inhibition of Pin1 in animal models has profound anti-tumor effects. In contrast, Pin1 is down-regulated or inactivated by multiple mechanisms in AD brains. The absence of Pin1 impairs tau function and amyloid precursor protein processing, leading to tangle- and amyloid-related pathologies and neurodegeneration in an age-dependent manner, resembling human AD. We have developed *cis* and *trans* conformation-specific antibodies to provide the first direct evidence that tau exists in distinct *cis* and *trans* conformations and that Pin1 accelerates its *cis* to *trans* conversion, thereby protecting against tangle formation in AD.
General significance: Available studies on Pin1 suggest that cancer and AD may share biological pathways that are deregulated in different directions. Pin1 biology opens exciting preventive and therapeutic horizons for both cancer and neurodegeneration. This article is part of a Special Issue entitled Proline-directed Foldases: Cell Signaling Catalysts and Drug Targets.

1. Introduction

The curious relationship between cancer and neurodegenerative diseases has drawn increasing attention as converging evidence suggests that one family of diseases provides protection against the other. This "inverse comorbidity" is unusual, and suggests that these conditions may share biological pathways which are deregulated in different directions [1]. We hypothesized over a decade ago that a predisposition to cancer might decrease the risk of AD based on our work with the protein Pin1, which plays a critical but opposite role in both diseases [2]. In this article we will show how the enzyme Pin1 is intimately involved in the pathogenesis of both cancer and AD, and serves as one molecular explanation of the inverse association between them.

We (KPL) originally identified Pin1 during a screen for anti-neoplastic agents as a human protein that can not only physically interact with the mitotic kinase NIMA, but also functionally suppress its ability to induce mitotic catastrophe in yeast [3]. Pin1 is now known to play an important role in many cellular processes, including the cell cycle and cell signaling, regulation of transcription and splicing, and maintenance of neuronal proteins including beta-amyloid and tau [4]. The Pin1 enzyme "twists" proteins into different shapes after proteins are phosphorylated on specific Ser or Thr residues preceding a Pro residue (pSer/Thr-Pro), so called Pro-directed phosphorylation [5,6].

Pro-directed phosphorylation is a major signaling mechanism in the cell [7–9]. The enzymes that are responsible for such phosphorylation are called proline-directed protein kinases, whose well-known members include mitogen-activated protein kinases (MAP kinases), cyclin-dependent kinases (CDKs) and glycogen synthase kinase-3 (GSK-3). Proline has an interesting stereochemistry due to the presence of a 5-membered ring on its peptide backbone. This allows it to flip between a *cis* or *trans* orientation, thereby changing the 3-D structure of the molecule. The recent identification of Pin1 as a

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peptidyl–prolyl *cis–trans* isomerase (PPIases) that specifically catalyzes *cis–trans* isomerization of certain pSer/Thr-Pro motifs led to the hypothesis of a new signaling mechanism, whereby Pin1 catalytically regulates the conformation of substrates after their phosphorylation to further control protein function [3,10–12]. Subsequent studies have shown that Pin1-catalyzed conformational regulation, which can now be detected by *cis* and *trans* conformation-specific antibodies [13], can have a profound impact on many key proteins involved in diverse cellular processes [2,14–17]. Pin1 has emerged as a novel molecular timer that modulates its multiple targets at various steps of a given cellular process to synergistically control the amplitude and duration of a cellular response or process [18]. Importantly deregulation of Pin1 has a major impact on the development of disease and offers attractive new therapeutic strategies, notably for treating cancer and Alzheimer's disease [14,19,20], the focus of this review.

2. Pin1 structure and function

The conformational significance of the pSer/Thr-Pro motif was not appreciated before the discovery of Pin1, which specifically catalyzes the *cis*/*trans* isomerization of specific pSer/Thr-Pro motifs (Fig. 1) [10]. It takes substantial energy to flip from *cis* to *trans* after phosphorylation, making it a naturally slow process. Pin1 accelerates this conformation change by over 1000-fold, and thus serves as a regulator of proline-directed phosphorylation [10,11,21]. Although there are a number of peptidyl–prolyl *cis–trans* isomerases (PPIases), Pin1 is the only one known so far that specifically targets the pSer/Thr-Pro sequence [22]. Pin1's specificity derives from its two-domain structure. The WW domain binds only to specific pSer/Thr-Pro motifs, while the PPIase domain catalyzes the conformational change [4]. The role of Pin1 in regulating pro-directed phosphorylation is illustrated in Fig. 2.

The changes in conformation catalyzed by Pin1 can affect a spectrum of substrate activities. The change in shape may serve as an "on–off" switch for target proteins—for example, by activating or deactivating an enzyme's catalytic site. Pin1 can also serve a "maintenance" role by returning proteins from a dysfunctional "*cis*" conformation back into functional "*trans*". In addition to affecting the shape and function of individual proteins, Pin1 has also been shown to act as a "molecular timer" that can act on many targets within a complex cellular process such as mitosis at different times and by multiple mechanisms [4]. Pin1's dual role in the regulation of cell signaling and maintenance of protein folding helps explain why its expression levels vary widely in different tissues. Pin1 usually has very low expression in cells that are not proliferating. Expression increases with cell proliferative capacity and Pin1 over-expression is seen in most human cancers [23–25]. Pin1 is also activated in cancer by post-translational modifications including dephosphorylation [26], phosphorylation [27,28] and desumoylation [29]. Pin1 activity is dramatically suppressed by the tumor suppressor gene BRCA-1 [30]. Pin1 catalytic activity and oncogenic function are also effectively suppressed by the tumor suppressor DAPK1 [15]. It is thus easy to see why Pin1 is tightly regulated in cells with mitotic potential. In stark contrast, Pin1 is highly expressed in neurons from the beginning of neuronal differentiation, suggesting that it serves a completely different purpose in these post-mitotic cells [31,32].

3. Pin1 and aging

Studies of Pin1-deficient mice suggest that it works to preserve cellular integrity in the face of aging. Pin1-knockout mice appear normal until about half-way through their lifespan, when they develop diffuse signs of premature aging, including neurodegeneration, osteoporosis, atrophy of skin and retina, loss of body mass, and accelerated telomere shortening (Fig. 3) [32–34]. There are a number of mechanisms by which Pin1 may help promote healthy aging through maintaining genomic integrity and regulating the cellular response to stress. The p53 gene is generally considered the "guardian of the genome" and can trigger senescence or apoptosis in response to DNA damage [35]. p53 is therefore a tumor suppressor and is commonly deleted or mutated in cancer cells. Pin1 preserves the function of p53 in the setting of response to DNA damage by preventing its degradation by the ubiquitin proteasome system [36,37]. It also enhances the DNA-binding activity of p53 to its targets, and is actually required to maintain the DNA damage checkpoints which allow cells to repair critical DNA damage [37].

Pin1 is also involved in the maintenance of telomeres—the critically important protective caps on the ends of linear chromosomes. Telomere shortening is related to many age-related diseases including some cancers, cardiovascular disease and neurodegeneration. Pin1 regulates the stability of the telomeric DNA-binding protein TRF1 [38]. When in its *cis*-conformation, TRF1 protein is stable and inhibits telomere elongation by binding to telomeres. Pin1 flips TRF1 into *trans*, TRF1 is susceptible to proteasome-mediated degradation, thereby allowing telomere elongation to occur via the enzyme telomerase. Pin1 also helps to limit oxidative damage by its negative regulation of the CDK inhibitor p27kip1 through binding to FOXO4, a protein involved in the response to mitochondrial and oxidative stress [39]. The fact that Pin1 is highly expressed in neurons and is oxidized and inactivated in the hippocampus of patients with MCI and AD [40,41] suggests that it may take part in the early response to oxidative stress. Together, these data point to Pin1 as a key regulator of healthy aging. As we will now see, these and other anti-aging properties of Pin1 have strong neuroprotective effects.

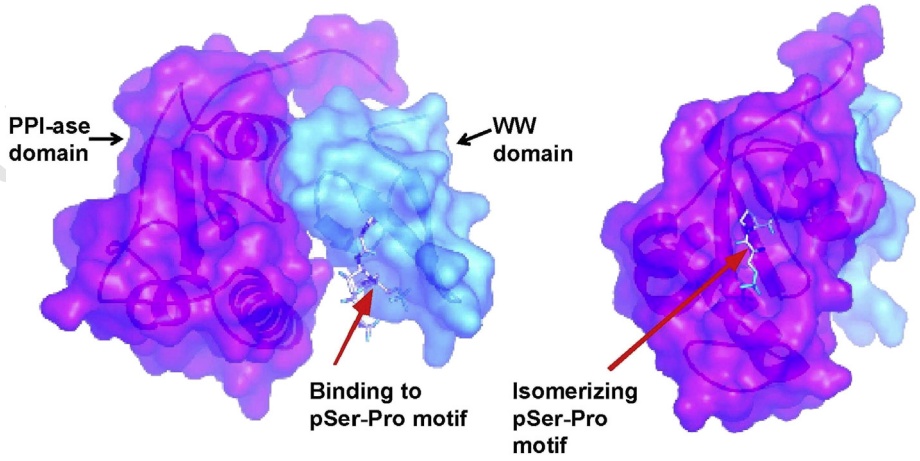

Fig. 1. Structure of Pin1: Pin1 has a unique substrate specificity that derives from its two domain structure. The WW domain specifically binds to the phosphorylated serine/threonine residue followed by a proline, and the PPI-ase domain flips the protein's orientation around the proline bond.

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