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Prolyl isomerase Pin1 and neurotrophins: a loop that may determine the fate of cells in cancer and neurodegeneration

Francesco Angelucci and Jakub Hort

Abstract: Increased survival, differentiation, and apoptotic death are common mechanisms relevant for both cancer and neurodegenerative diseases. Although these disorders are characterized by different manifestations, it appears that a common mechanism may be present which directs the fate of a cell to either degeneration or proliferation. There are two classes of proteins that have been extensively investigated in these diseases but their possible interaction during signal transduction has not been studied. Prolyl isomerase Pin1 is an enzyme which translates Ser/Thr-Pro phosphorylation into conformational changes able to modify the activities of its substrates. Its role in cancer development has been linked to its capacity to induce conformational changes to the tumor suppressor gene p53. Neurotrophins belong to a family of proteins that induce opposite effects on neuronal cells such as increased survival, development, and function. According to their function, alteration of these proteins during neurodegenerative processes has been investigated and reported in a number of experimental paradigms involving animal models and humans. However, in recent years, it has been shown that Pin1 downregulation is present in neurodegenerative disorders, while increased expression of neurotrophins and their receptors is found in certain types of cancer and correlate with poor prognosis. Notably, at the level of signal transduction, Pin1 and neurotrophin activity regulate the outcome of similar pathways such as proline-directed kinase and, most importantly, p53 signaling. Thus the possible existence of a loop between Pin1 and neurotrophins was investigated to understand the pathogenesis of these diseases.

Keywords: cancer, neurodegeneration, neurotrophins, p53, Pin1

Introduction

Recent epidemiological studies have shown an inverse association between the occurrence of cancer and Alzheimer's disease (AD) [Ma *et al.* 2014; Musicco *et al.* 2013], supporting the idea that a common mechanism may be present and directs the fate of a cell to either degeneration or proliferation. Nevertheless, so far this mechanism has not been discovered.

The prolyl isomerase Pin1 in cancer and Alzheimer's disease

Prolyl isomerase Pin1 is a unique enzyme that changes the shape of target proteins by acting on specific amino acids that have been phosphorylated; serine or threonine residues that precede proline [Lu and Zhou, 2007]. Pin1 has been identified as a regulator of phosphorylation signaling in several types of cancer, including breast, gastric, lung, esophageal, head and neck squamous cell carcinoma, and laryngeal squamous cell cancer. In these types of cancer, Pin1 is either over expressed or present with genetic variants in the Pin1 gene [Finn and Lu, 2008]. This promoting action of Pin1 in cancer has also been associated with its capacity to inhibit some tumor suppressor genes, such as RUNX3 and p53 [Hu and Wulf, 2011; Nicole Tsang *et al.* 2013]. While in normal conditions Pin1 promotes the activity of oncogenes such as p53, in pathological conditions this regulatory mechanism accelerates malignant transformation when the oncogene carries a dominant negative mutation [Hu and Wulf, 2011].

Correspondence to:
Francesco Angelucci, PhD
Department of Clinical and Behavioral Neurology, IRCCS Santa Lucia Foundation, 00179, Rome, Italy
f.angelucci@hsantalucia.it

Jakub Hort, MD, PhD
Memory Clinic, Department of Neurology, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, and International Clinical Research Center, St Anne's University Hospital Brno, Brno, Czech Republic

Interestingly, it has been shown that Pin1 alterations are also present in pathologies characterized by neurodegenerative processes such as AD [Pastorino *et al*. 2012]. This field of research is still ongoing but present evidence shows that there is a downregulation in the expression of Pin1 in neurons and that this event may be part of the pathogenic mechanism in AD. Although its role in neurons is still unclear, Pin1 is known to regulate a number of important proteins, including tau and amyloid precursor (APP) proteins. In contrast to cycling cells, neuronal expression of Pin 1 increases during differentiation and remains elevated throughout the lifespan [Liou *et al*. 2003]. Moreover, overexpression of Pin1 in mature neurons protects against neurodegeneration induced by tau overexpression [Lim *et al*. 2008]. Pin1 knockout mice develop a premature age-dependent neurodegeneration similar to AD in humans characterized by tau hyperphosphorylation and an increase in the pathogenic processing of APP [Liou *et al*. 2003; Pastorino *et al*. 2006].

These studies indicate that Pin1 activity has a dual role in cells. It may favor proliferation or induce cell death depending on the circumstances, which may include multiple mechanisms, such as gene transcription and protein phosphorylation. Pin1 can thus serve as a molecular 'timer' or 'switch', turning proteins or entire pathways 'on' or 'off' at critical times.

Neurotrophins in cancer and Alzheimer's disease

There is another class of protein which resembles the action of Pin1 at cellular level. These proteins, named neurotrophins, play a pivotal role in cell survival, and the development and function of the neurons. The neurotrophin family includes at least four members: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4). The action of neurotrophins is mediated by binding to the tyrosine kinase (Trk) family of receptors (including TrkA, TrkB, and TrkC), and to the p75 receptor (p75NTR), a member of the tumor necrosis factor receptor family [Huang and Reichardt, 2001].

Neurotrophins not only regulate the survival of neurons undergoing neurodegeneration in AD, but also (in the case of BDNF) synaptic plasticity, the process through which a neuron responds and adapts to a new situation in its environment. In humans, postmortem studies have shown that neurotrophin brain levels are reduced in AD, supporting the notion that these proteins are neuroprotective and may have a potential role in the treatment of neurodegenerative disorders.

Neurotrophin signaling through the Trk receptor mainly induces three intracellular signaling pathways: inhibition of programmed cell death (apoptosis), induction of growth arrest, and promotion of neurogenesis. Interestingly, in recent years it has become evident that the survival-promoting action of neurotrophins may sustain certain types of cancer. There are several reasons why neurotrophins can also play a role in cancer. First of all, the Trk receptor was first described as proto-oncogene and the receptor for NGF TrkA was found to be downregulated in neuroblastoma with aggressive behavior [Nakagawara *et al*. 1993], suggesting that this kind of tumor may require the presence of NGF for survival and may regress in its absence. This concept has been further developed leading to the hypothesis that the Trk receptor system may represent a bridge between cancer and neuronal development in brain tumors such as neuroblastoma and medulloblastoma [Nakagawara, 2001]. Furthermore, the involvement of NGF, BDNF, NT-4/5 and their receptors has been demonstrated in other types of cancer, such as breast and lung cancer. Notably in these tumors, *in vitro* and *in vivo* experiments have shown that stimulation of neurotrophin and the Trk receptors can result in cellular growth [Nakagawara, 2001; Sinkevicius *et al*. 2014], while preclinical studies demonstrated that targeting neurotrophins and/or their receptors induces an inhibition of cancer cell survival, proliferation, and invasion [Hondermarck, 2012].

Signal transduction

Summarizing the experimental evidence reported, it appears that the pattern of changes in neurotrophin and Pin1 expressions in cancer and neurodegeneration are comparable. Accordingly, tentative explanations for AD–cancer 'inverse comorbidity' have been proposed with both Pin1 [Driver *et al*. 2015] and neurotrophin dysregulation [Krüttgen *et al*. 2006]. The possible relationship between neurotrophins and Pin1 can be depicted further by analyzing the signal transduction pathways activated by these proteins. Neurotrophins and Pin1 share

important mechanisms in cells. During their survival-promoting activity, neurotrophins and Pin1 may activate proline-directed kinase signaling and consequently regulate cell proliferation and survival. These pathways include mitogen-activated protein kinases, nuclear factor kappa-light-chain-enhancer of activated B cells, glycogen synthase kinase 3, and others. Also, during their apoptotic promoting action, similar pathways can be activated, such as c-Jun N-terminal kinase. In addition, neurotrophins and Pin1 can both influence the expression of p53, which is considered to be a tumor suppressor but it has also been proposed that it has a novel role in neuronal differentiation, axon guidance, neurite outgrowth, and axonal regeneration [Tedeschi and Di Giovanni, 2009].

Pin1 and neurotrophins

Pin1 and neurotrophins may act synergistically and determine the fate of cells with regard to neuronal survival or neuronal death, and this mechanism is may be part of the pathogenic mechanism connecting cancer and neurodegenerative disorders, at least AD. Going further, we suggest that Pin1 might be required for the signal transduction pathways activated by Trk receptors, thus modulating neurotrophin activity.

A possible scenario(s) on how Pin1 affects neurotrophin activity is now described. As stated before, Pin1 is the only known isomerase that specifically catalyzes the phosphorylated pThr/pSer-Pro motifs from cis-configuration to trans-configuration. Induction of serine/threonine kinase activity is critical for cell survival and proliferation, and is part of the signal transduction cascade of neurotrophins. Specifically, among the pathways activated by neurotrophins through the Trk receptors, a survival pathway includes the activation of the serine/threonine protein kinase B (also known as Akt).

Akt plays an essential role in cell survival, growth, migration, and proliferation, Altered Akt activity has been associated with cancer and other disease conditions, including neurodegenerative diseases. Recent reports have shown that the stability of Akt protein is regulated through phosphorylation on its Thr-Pro motifs and that Pin1 is a crucial factor for Akt stability and activation phosphorylation [Liao *et al.* 2009]. By this mechanism Pin1 can be a molecular 'timer' or 'switch', turning neurotrophin pathways 'on' or 'off'.

Moreover, Pin1 has a central role in transducing phosphorylation of p53 into conformational changes that affect p53 stability and function. p53 is not only a tumor suppressor but it integrates a number of extracellular signals that involve neurotrophins. For example, p53 gene silencing or dominant negative forms of p53 that inhibit p53 transactivation capacity block NGF-dependent neurite outgrowth in PC-12 cells, thereby showing a direct requirement for p53 in neuronal differentiation and outgrowth. Thus p53 is necessary for the action of neurotrophins and may contribute to neuronal development through the regulation of gene targets distinct from its known transcriptional targets for apoptosis or DNA repair [Brynczka *et al.* 2007]. Given its role in regulating p53 conformational changes, Pin1 may be the factor that can drive p53 to be responsive to the action of neurotrophins during either cancer or neurodegenerative processes. When Pin1 is overexpressed in cancer, it may stimulate the Trk receptor-mediated pathways of neurotrophins and, at the same time, induce conformational changes of p53 in its survival-promoting direction. On the other hand, during neurodegenerative processes, low expression of Pin1 may be the cause of reduced functionality of the neurotrophin–Trk system and p53 survival action, with the result of favoring neuronal death.

Possible physiologic and therapeutic implications

If inhibition or stimulation of Pin1 may cause an alteration in neurotrophins or their receptor levels and/or their functionality, this may introduce the possibility of modulating these proteins epigenetically and not by exogenous administration, the method investigated most so far. The fact that epigenetic mechanisms, such those regulated by Pin1, are reversible as opposed to genetic modification, is even more intriguing. Nonetheless, it is clear that the loop between Pin1 and neurotrophin needs to be in equilibrium, otherwise favoring one (cancer) or the other (neurodegenerative disorders) pathological process.

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