Pin1 in Alzheimer’s disease

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Abstract
Proteolytic processing and phosphorylation of amyloid precursor protein (APP), and hyperphosphorylation of tau protein, have been shown to be increased in Alzheimer’s disease (AD) brains, leading to increased production of β-amyloid (Aβ) peptides and neurofibrillary tangles, respectively. These observations suggest that phosphorylation events are critical to the understanding of the pathogenesis and treatment of this devastating disease. Pin-1, one of the peptidyl-prolyl isomerases (PPIase), catalyzes the isomerization of the peptide bond between pSer/Thr-Pro in proteins, thereby regulating their biological functions which include protein assembly, folding, intracellular transport, intracellular signaling, transcription, cell cycle progression and apoptosis. A number of previous studies have shown that Pin1 is co-localized with phosphorylated tau in AD brain, and shows an inverse relationship to the expression of tau. Pin1 protects neurons under in vitro conditions. Moreover, recent studies demonstrate that APP is a target for Pin1 and thus, in Aβ production. Furthermore, Pin1 was found to be oxidatively modified and to have reduced activity in the hippocampus in mild cognitive impairment (MCI) and AD. Because of the diverse functions of Pin1, and the discovery that this protein is one of the oxidized proteins common to both MCI and AD brain, the question arises as to whether Pin1 is one of the driving forces for the initiation or progression of AD pathogenesis, finally leading to neurodegeneration and neuronal apoptosis. In the present review, we discuss the role of Pin1 with respect to Alzheimer’s disease.

Keywords: Alzheimer’s disease, amyloid beta-peptide, apoptosis, cell cycle, cell signaling, hyperphosphorylated tau, peptidyl-prolyl cis/trans isomerases.


The major histopathological characteristics of Alzheimer’s disease (AD) are the deposition of senile plaques, accumulation of intracellular neurofibrillary tangles (NFT), synapse loss and oxidative neuronal damage (Katzman and Saitoh 1991; Markesbery 1997; Butterfield and Lauderback 2002). Amyloid β-peptide (Aβ), the main component of senile plaques and a 39–43 amino acid peptide derived from amyloid precursor protein (APP), is thought to be the principle agent responsible for AD pathogenesis (Katzman and Saitoh 1991; Kerr and Small 2005). NFT are largely composed of neuronal cytoskeleton components, i.e. hyperphosphorylated tau and neurofilament proteins (Grundke-Iqbal et al. 1986).

One proposed mechanism of Aβ-induced neuronal toxicity is the generation of oxidative stress (Butterfield and Stadtman 1997; Markesbery 1997; Butterfield and Kanski 2001; Butterfield and Lauderback 2002) occurring as the result of an imbalance between reactive oxygen species (ROS), reactive nitrogen species (RNS) and cellular oxidant defenses. The ROS and RNS could react with a number of cellular macromolecular targets, including proteins, lipids, carbohydrates, DNA and RNA. The early markers of oxidative stress in a cell include the formation of protein carbonyls, HNE, and 3-NT (Butterfield 2002; Smith et al. 1996, 1997; Lovell

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Abbreviations used: Aβ, β-amyloid peptide; AD, Alzheimer’s disease; APP, amyloid precursor protein; cdk, cyclin-dependent kinase; CTD, C-terminal domain; MCI, mild cognitive impairment; NF-κB, nuclear factor kappa B; NFT, neurofibrillary tangles; PPIases, peptidyl-prolyl cis/trans isomerases; RNS, reactive nitrogen species; ROS, reactive oxygen species.

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et al. 2001; Butterfield and Lauderback 2002; Castegna et al. 2003). Protein oxidation has been correlated with the pathophysiology of AD (Castellani et al. 2000; Smith et al. 1994). In the AD brain, levels of protein carbonyl were found to be elevated (Smith et al. 1994; Aksenov et al. 2001) in a region-specific manner; protein oxidation was reported to be greater in Aβ-rich regions like the cortex and hippocampus, but it was not observed in the cerebellum where Aβ was found to be negligible (Hensley et al. 1995). In addition, the use of Vitamin E diminished Aβ (1–42)-induced toxicity in cell cultures and supports the role of oxidative stress in AD pathology (Yatin et al. 2000; Butterfield 2002; Boyd-Kimball et al. 2004).

In AD, hyperphosphorylation of tau has been shown to precede tangle formation and neurodegeneration (Lee and Tsai 2003; Lu et al. 2003). Further, phosphorylation of APP on the Thr668-Pro motif has been shown to be increased in AD brain or in models of AD, leading to increased production of Aβ peptides (Lee et al. 2003; Pastirino et al. 2006). These studies suggest that phosphorylation events are critical to the understanding of the pathogenesis and treatment of this devastating disease. Tau protein plays an important role in tubulin polymerization and the stabilization of microtubules, thereby maintaining the neuronal cytoskeleton (Daly et al. 2002; Mandelkow et al. 2003). The hyperphosphorylation of Tau leads to the disruption of vital cellular processes, such as axonal transport mechanisms and loss of cell shape, and also leads to the degeneration of affected neurons. This binding function of Tau to tubulin is regulated by phosphorylation. Tau phosphorylated at certain sites can detach from microtubules so that they become more labile and dynamic. The hyperphosphorylation of tau protein could be related to unbalanced kinase or phosphatase activities, which are further regulated by other proteins like Pin1 (peptidyl-prolyl cis/trans isomerase) (Wang et al. 1995; Sze et al. 2004). As described more fully below, our laboratory first identified Pin1 as an oxidized protein, using a redox proteomics approach in hippocampus, in both AD and mild cognitive impairment (MCI); we also reported a decreased activity of Pin1, suggesting a possible link between oxidative stress of key proteins and the mechanisms for neurodegeneration in AD brain (Sultana et al. 2005, 2006; Butterfield et al. 2006a).

Peptidyl-prolyl cis/trans isomerases (PPIases EC 5.2.1.8) are classified into three families: cyclophilin PPIase, FK506 PPIase and parvulin. Cyclophilin and FK506 are inhibited by cyclophilin and FK506 (Galat 2003; Kay 1996), respectively, whereas both these inhibitors have no effect on the parvulin family of PPIases (Ruten et al. 1999). The ubiquitous PPIase, Pin1, belongs to the parvulin family; it is conserved from yeast to humans and has been shown to be necessary for entry into mitosis (Lu et al. 1996; Shen et al. 1998). The yeast homologue, Ess1, is essential for cell survival (Devashayam et al. 2002). Pin1 differs from other PPIases because it only isomerizes the bond between pSer/Thr-Pro while the substrates for other PPIases are unphosphorylated (Lu et al. 1996; Ranganathan et al. 1997; Yaffe et al. 1997; Schutkowski et al. 1998). This phosphorylation-dependent interaction targets Pin1 to a defined subset of phosphorylated substrates facilitating conformational changes in phosphorylated proteins, thereby regulating their biological functions, which include protein assembly, folding, intracellular transport (Kay 1996; Gothel and Marahiel 1999; Schiene and Fischer 2000), intracellular signaling, transcription, cell-cycle progression and apoptosis (Lu et al. 1996; Crenshaw et al. 1998; Hunter 1998; Chen et al. 1997; Albert et al. 1999; Morris et al. 1999; Wu et al. 2000) (Fig. 1). Thus, Pin1-dependent prolyl isomerization is an essential post-phosphorylation regulatory mechanism (Liou et al. 2002) that may provide a novel signaling mechanism for regulating the dephosphorylation of specific targets in subcellular compartments, thereby mediating the control of a range of cellular activities (Zhou et al. 1999; Lu et al. 2002). So far, more than 35 Pin1-binding proteins have been identified and many more remain to be elucidated (Lu 2004).

The implications of Pin1 in AD pathogenesis have been reported from several laboratories (Lu et al. 1999b; Hammond et al. 2002, 2003; Liou et al. 2003; Ramakrishnan et al. 2003). The recent finding that Pin1 is oxidatively modified, and that it also shows reduced activity and decreased expression in hippocampus from MCI and AD subjects (Butterfield et al. 2006a; Sultana et al. 2005, 2006), has suggested important consequences related to the progression of AD. The diverse functions of Pin1, and the observation that this protein is one of the oxidized proteins common to both MCI and AD brain, raises the question as to whether dysfunctional Pin1 is a major driving force for the initiation or progression of AD pathogenesis, finally leading to neurodegeneration and neuronal apoptosis (Fig. 2). Furthermore, previous studies have shown that Pin1 is co-localized with phosphorylated tau and exists in inverse relationship to the expression of tau in AD (Holzer et al. 2002; Ramakrishnan et al. 2003). In addition, an in vitro study has shown that Pin1 protects neurons against age-related neurodegeneration (Liou et al. 2003); it can also restore the ability of phosphorylated tau to bind microtubules and promote their assembly in vitro, a process that might represent a potential therapeutic use for Pin1 (Thorpe et al. 2001).

Pin1 is mainly localized to neuronal nuclei in normal human brain but in AD brain, it is found in neuronal cytoplasm and perikaryon NFTs. Pin1 in AD brain binds to the phosphorylated Thr231 residue of tau protein. This Pin1 binding to p-tau in NFTs is redirected to the cytoplasm of NFT-containing neurons, leading to decreased availability of soluble Pin1 protein (Thorpe et al. 2004). The neurodegeneration and neuronal apoptosis in AD might conceivably be induced via depletion of nuclear Pin1 or association with...
specific up-regulated phosphoprotein targets, such as Bcl-2 (Pathan et al. 2001) and p53 (Lu et al. 1996; Wulf et al. 2002; Zacchi et al. 2002; Zheng et al. 2002; Lavoie et al. 2003; Thorpe et al. 2004).

**Pin1 structure and function**

Pin1 protein has two domains (Fig. 3), a carboxy-terminal, PPIase domain responsible for isomerization and an amino-terminal, WW domain that is the binding element specific for

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pSer/Thr-Pro motifs. The WW domain is surrounded by multiple upstream hydrophobic residues, such as isoleucine, valine, tyrosine and/or phenylalanine, and a downstream arginine or lysine residue (Yaffe et al. 1997; Lu et al. 1999b; Verdecia et al. 2000; Lu 2004; Smet et al. 2005). Lys63, Arg68 and Arg69 are crucial for enzyme function and are involved in the sequestering of the pSer/Thr (Lu 2004). The WW domain binds linear peptide motifs due to its shallow interface. The WW domain is composed of an anti-parallel, three-stranded β-sheet flanked by Trp11 and Trp34 (Verdecia et al. 2000). The dissociation constant for the binding of pSer/Thr-Pro is approximately 50 μM, but it can be improved by a substrate with a consensus strand of Pro-X-pSer/Thr-Pro if X is not glycine. The binding is maintained by a combination of hydrogen bonding and Van der Waals forces. A water molecule is also used to modulate the hydrogen combination of hydrogen bonding and Van der Waals forces.

Role of Pin1 in cell-cycle regulation

In most cells, including neurons, Pin1 is predominantly nuclear (Lu et al. 1996) and Pin1 activity is required for the DNA replication checkpoint (Winkler et al. 2000). Pin1 regulates the activity of a subset of mitotic and nuclear proteins in a phosphorylation-dependent manner (Yaffe et al. 1997; Shen et al. 1998). Many studies have shown that improper activation of mitotic events in the cell cycle may contribute to the hyperphosphorylation of tau protein, thereby playing an important role in the progression of AD (Vincent et al. 1996; Yaffe et al. 1997; Nagy et al. 1998; Raina et al. 1999; Husseman et al. 2000; Vincent 2000). By subsequent isomerization and dephosphorylation of tau, Pin1 is able to restore the function and conformation of phosphorylated tau, thereby regulating mitotic events (Lu et al. 1999a; Zhou et al. 2000).

It is still not clear why terminally differentiated neurons in the G0 phase of the cell cycle enter the G1 phase of mitosis and become stuck at the G2 phase, leading to apoptosis in AD, but it is evident from recent findings that certain key cell cycle-regulating proteins, such as cyclin-dependent kinases (cdks) that are dependent on Pin1-mediated isomerization, are expressed in AD neurons (Husseman et al. 2000; Tomashevski et al. 2001; Vincent et al. 2001). Activation of cyclin B/Cdc2 leads to phosphorylation of many proteins, such as Cdc25c, Wee1 and tau, at multiple Ser/Thr-pro sites that are key mitotic regulators (Davis et al. 1983; Matsu moto-Taniura et al. 1996; Stukenberg et al. 1997; Yaffe et al. 1997). Evidence for the appearance of cell-cycle proteins in AD brain exists. For example, mitotic Cdc2 kinase is found in AD brain and this kinase co-precipitates with its activator, cyclin B1 (Vincent et al. 1997), which phosphorylates tau. Also, enzymes activating Cdc2 are active in AD brain, and activities of Cdc2 activators, such as Cdc25, are increased while the activity of Wee1, an inhibitor of Cdc2, is decreased (Ding et al. 2000a; Tomashevski et al. 2001). Dephosphorylation of these regulators is catalyzed by the Pin1-dependent phosphatase, PP2A, which dephosphorylates at conserved pSer/Thr-Pro sites (Lee et al. 1991; Che et al. 1998). PP2As are conformation-specific phosphatases that catalyze dephosphorylation of trans pSer/Thr-Pro sites of Cdc25c and tau, which, as noted above, are key mitotic regulators in the cell cycle (Zhou et al. 2000). Pin1 mediates conversion of cis pSer/Thr-Pro to trans and facilitates dephosphorylation by PP2A (Zhou et al. 2000).

Hyperphosphorylation of tau in NFT is a prominent pathological hallmark in AD. Furthermore, PP2A, a physiological tau phosphatase, is associated with microtubules (Sontag et al. 1996), and Pin1-induced prolyl isomerization facilitates tau dephosphorylation by PP2A (Zhou et al. 2000). Hence, Pin1 can indirectly restore the function of phosphorylated tau by promoting its dephosphorylation by PP2A. Conversely, we postulate that oxidative dysfunction of Pin1 (Sultana et al. 2003, 2006; Butterfield et al. 2006a) would lead to the loss to PP2A-mediated dephosphorylation of tau, with consequent neuronal dysfunction.

Role of Pin1 in the cytokine–NF-Kappa B pathway

The transcriptional regulator, nuclear factor kappa B (NF-κB), appears to stimulate the expression of specific protective genes. However, the identities of these genes in anti-apoptotic processes are unknown. NF-κB signaling is activated by 1 kappa B kinase (IKK)-mediated phosphorylation, followed by the degradation of its inhibitor, IκBα, which can then translocate to the nucleus and activate target genes (Santoro et al. 2003). It has recently been demonstrated that active Pin1 can bind to the specific trans pSer/Thr-Pro motifs via its WW domain and catalyze the trans to cis conversion (Ryo et al. 2003). The resulting cis conformation, which is stable and might be protected from dephosphorylation or degradation, is a regulatory mechanism of nuclear NF-κB (Ryo et al. 2003). Upon cytokine treatment, Pin1 binds to phosphorylated p65 and inhibits p65 binding to IκBα, resulting in increased nuclear accumulation and protein stability of p65, and enhanced NF-κB activity. Furthermore, in Pin1-deficient mice, cells are refractory to NF-κB activation by cytokine signals (Ryo et al. 2003).

Cytokine-induced inflammation is characteristic of neurodegenerative diseases such as AD (Butterfield et al. 2002; McGeer et al. 2005; Mrak and Griffin 2005). Neuropathological evidence of activated microglia and astrocytes in lesioned areas, combined with epidemiological evidence of...
decreased risk of AD in long-term users of anti-inflammatory agents, suggests that inflammation is autodestructive of neurons (McGeer et al. 2005). Aβ (1–42) peptide, as well as hyperphosphorylated tau protein, strongly activate NF-κB-DNA binding via ROS in both neuroblastoma and cerebellar granule cells (Behl et al. 1994; Kaltschmidt et al. 1994, 1997). NF-κB-DNA binding correlated to high COX-2 RNA message abundance in both control and AD samples, suggesting that NF-κB-related, inflammatory mechanisms operate during aging, and in human neocortex undergoing neurodegeneration.

Role of Pin1 in transcription

RNA polymerase II has long been known to be responsible for transcription of mRNA-encoding genes. The mRNA participates in post-transcriptional events (Hirose and Manley 2000; Maniatis and Reed 2002; Orphanides and Reinberg 2002). The C-terminal domain can be extensively phosphorylated, especially at the Ser2 and Ser5 positions, which results in two distinguishable forms of RNA polymerase II, the hyperphosphorylated IIO and hypophosphorylated IIA forms (Corden 1993; Dahmus 1996). It has been reported that the IIA form interacts with the promoter to form a stable pre-initiation complex, and entry to initiation of transcription is accompanied by C-terminal domain (CTD) phosphorylation (Payne et al. 1989; Zawel and Reinberg 1992; Corden 1993; Dahmus 1994; O’Brien et al. 1994). By the completion of transcription, the IIO form must be dephosphorylated to regenerate the IIO form and complete the cycle (Dahmus 1996). The regulation of the CTD structure could be an important aspect of mRNA production. The CTD acts as a platform for coupling mRNA processing to transcription in order to recruit splicing, polyadenylation and capping factors to the transcription complex (Cho et al. 1997; McCracken et al. 1997; Steinmetz 1997). The modulation of the phosphorylation state of the CTD with transcription and mRNA processing factors, multiple kinases and phosphatases (Dahmus 1994, 1996; Archambault et al. 1998) regulates transcriptional and post-transcriptional events by catalyzing phosphorylation-dependent conformational changes of the large subunit of RNA polymerase II (Albert et al. 1999).

The transition from initiation to elongation is accompanied by CTD phosphorylation, predominantly on Ser5, by the cdk7 component of the general transcription factor, TFIIH (Komarnitsky et al. 2000; Schroeder et al. 2000). During elongation, the phosphorylation pattern changes towards Ser2 phosphorylation (Cho et al. 2001). This involves different cdks, such as the cdk9 subunit of the elongation factor, p-TEFβ (Price 2000). Formation of a carboxy-terminal domain phosphatase 1 is one of several CTD kinases (Chambers and Dahmus 1994; Cho et al. 1999), which presumably helps to recycle RNA polymerase II at the end of the transcription cycle by converting RNA polymerase IIO into IIA for another round of transcription.

The CTD of RNA polymerase II is a target of Pin1, and Pin1 can interact with transcription factors, such as phosphorylated c-Jun and β-catenin, and increase their activities in transcription of the cyclin D1 gene (Ryo et al. 2001; Wulf et al. 2001). Pin1 inhibits CTD dephosphorylation by FCP1 and stimulates its phosphorylation by the cdk, cyclin B, in vitro. Thus, Pin1 plays a significant role in regulating the activities of the CTD. Interestingly, cyclin D1 knock-out mice showed several prominent phenotypes, including retinal degeneration and mammary gland impairment (Fantl et al. 1995; Sicinski et al. 1995). Pin1 directly bound to, and stabilized cyclin D1 in the nucleus, indicating that Pin1 regulates stability and subcellular localization of cyclin D1 to the transcriptional regulation of the cyclin D1 gene (Ryo et al. 2001; Wulf et al. 2001). Pin1 facilitates C-terminal dephosphorylation in yeast and in vitro (Wu et al. 2000; Kops et al. 2002), but increases phosphorylation of the CTD in mammalian mitotic cells (Xu et al. 2003). Recent studies have also demonstrated that Pin1 regulates centrosome duplication and implies a role of Pin1 in cancer (Suizu et al. 2006).

Role of Pin1 in AD apoptosis and DNA damage response

There is an increasing consensus that apoptosis plays a significant role in the mechanism of neurodegeneration and cell death observed in affected neurons in AD (Anderson et al. 2000; Czech et al. 2000; Eckert et al. 2003; Tacconi et al. 2004). Though neurons of the adult brain are normally considered to be in a ‘terminally differentiated’ state, accumulation of mitotic phosphoepitopes through the re-expression and activation of the mitotic phase regulating kinase and associated cell cycle-related proteins, e.g. Cdc25A and polo-like kinase (Plk1), has been shown in AD (Ding et al. 2000b; Harris et al. 2000). The observations that a number of mitotic proteins have increased expression and the fact that Pin1 is oxidatively modified are consistent with the notion that oxidative dysfunction of Pin1 could be related to AD neurons entering the cell cycle, and subsequent apoptosis. The re-entry into the cell cycle in AD causes the abnormal hyper-phosphorylation of the tau protein, a key component of the neuronal cytoskeleton and a known target for Pin1 that maintains the normal function of microtubules (Lu et al. 1999a; Arendt et al. 2000).

Following re-entry into the cell cycle, induction of mitosis and activation of kinases, anti-apoptotic protein Bcl-2 is thought to be transiently phosphorylated, leading to inactivation of its anti-apoptotic activities and making it a target for Pin1 (Srivastava et al. 1998; Yamamoto et al. 1999).

Though not shown in AD, it is suggested that the binding of pBcl-2 and Pin1 causes a conformational change in which phosphatases, such as PPA2, become accessible to the pBel...
increased DNA and protein damage induced by oxidative stress (Mattson 2005). It has been shown that in AD, there is decreased binding to, and destabilization of, microtubules, resulting in inhibition of axonal transport, starvation of synapses for energy, and eventual synapse loss and neuronal death.

Pin1 is required for protecting the cell from DNA damage-induced apoptosis (Wulf et al. 2002; Zheng et al. 2002). However, Pin1 can also accelerate apoptosis by enhancing pro-apoptotic genes (Zacchi et al. 2002). Indeed, protective strategies against neuronal apoptosis related to Aβ (1–42) may be different between intracellular (Magrane et al. 2004) and extracellular Aβ (1–42) (Zhang et al. 2003). These discrepancies might reflect the fact that, depending on the conditions of the cell and DNA damage, p53 can induce apoptosis (Wahl and Carr 2001). Further studies are required to define the physiological and pathological roles of Pin1-mediated p53 regulation in AD.

**Pin1 is oxidatively inactivated in MCI and AD brain**

Elevated oxidative damage to proteins and lipids occurs in AD brain, as noted above (Butterfield and Lauderback 2002). Moreover, we recently demonstrated that MCI brain had increased protein oxidation and lipid peroxidation (Keller et al. 2005; Butterfield et al. 2006a,b). Pursuing these results, redox proteomics (Dalle-Donne et al. 2006) was used to identify Pin1 as oxidatively modified in hippocampus in both MCI and AD (Sultana et al. 2005, 2006; Butterfield et al. 2006a). Moreover, building on previous studies which showed that oxidatively modified proteins were generally dysfunctional (Hensley et al. 1995; Perluigi et al. 2005; Poon et al. 2005a,b,c,d), measurement of the activity of Pin1 in MCI and AD brain showed decreased activity compared with age-matched normal controls (Sultana et al. 2006; Butterfield et al. 2006a). In separate experiments, if purified Pin1 was oxidized in vitro, its activity declined (Sultana et al. 2006). Hence, oxidative inactivation of Pin1 could have profound effects in AD and MCI brain, as outlined above (Figs 1 and 2). In particular, given the role of Pin1 in regulating the production of Aβ (Pastorino et al. 2006) and dephosphorylation of tau (Lee and Tsai 2003; Lu et al. 2003), we propose that oxidative dysfunction of Pin1 is involved in two of the primary pathological hallmarks of AD brain, senile plaques and NFT.

**Conclusions**

Pin1 is a phosphorylation-specific PPIase that is closely involved in a wide variety of cellular functions. In AD brain, depletion of Pin1 (Lu et al. 1996, 1999a), or oxidative modification and subsequent inactivation of Pin1 (Sultana et al. 2005, 2006; Butterfield et al. 2006a), may lead to accumulation of phosphorylated tau protein leading to NFT formation, and may lead to elevated Aβ. In its oligomeric form, Aβ (1–42) oxidizes proteins (Drake et al. 2003) and leads to memory and learning deficits (Lesne et al. 2006). Thus, Pin1 may be intimately involved in the progression of AD. The identification of the Pin1 protein as a common target of oxidation and subsequent dysfunction in AD and MCI brain (Sultana et al. 2005, 2006; Butterfield et al. 2006a) suggests the possible involvement of this protein in...
AD pathogenesis, and that it is potentially involved in the conversion of MCI to AD. Combinatorial approaches have led to potent Pin1 inhibitors (Wildemann et al. 2006). Among the challenges for future research on Pin1 is the determination of whether potent protective agents for Pin1 against oxidative modification can be developed, and whether such agents protect patients with MCI against conversion to AD. Studies to evaluate the potential of Pin1 as a therapeutic target in neurodegeneration, and models thereof, are in progress in our laboratory.

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