Review Article

c-Abl Inhibitors: A multifaceted approach for Parkinson's disease

Aarushi Sharma, Kanchan Kashyap and Vivek Sharma*

Government College of Pharmacy, Rohru, Distt Shimla-171207, Himachal Pradesh, India

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Abstract

Parkinson's disease (PD) is one of the most common neurodegenerative syndrome manifested by rest tremors, rigidity, bradykinesia and postural instability. PD can also be associated with neurobehavioral complications (depression, anxiety), cognitive impairment (dementia) and autonomic dysfunction (orthostasis and hyperhidrosis). Typical neuropathological features of PD include degeneration of dopaminergic neurons located in the pars compacta of the substantia nigra that project to the striatum (nigro-striatal pathway) and depositions of cytoplasmic fibrillary inclusions (Lewy bodies) which contain ubiquitin and alpha-synuclein. Enormous progress has been made in the treatment of PD yet, Levodopa beside having complications like wearing off phenomenon, levodopa-induced dyskinesias (peak-dose dyskinesias, biphasic dyskinesias) and other motor complications remains the most potent drug for controlling PD symptoms. Catechol-o-methyl-transferase inhibitors, dopamine agonists and nondopaminergic therapy are other alternative modalities in the management of PD and may be used concomitantly with levodopa or one another. The neurosurgical treatment and stem cell therapy are other options but current clinical treatments for PD mainly focus on suppressing disease symptoms rather than restricting disease progression. Thus a quest to find a drug which not only cures complications but stops disease progression is yet to be met. In this line the c-Abl tyrosine kinase inhibitors has shown a great promise. cAbl participates in a variety of cellular functions, including regulation of the actin cytoskeleton, regulation of the cell cycle and the apoptotic/cell cycle arrest response to stress beside playing a crucial role in development of the central nervous system. Recent studies have shown c-Abl activation in Parkinson's disease and suggests that therapies that block c-Abl could potentially change the course of the disease. These findings are especially timely because a c-Abl blocker called nilotinib has been proved successful in several animal models for PD.

Keywords: cAbl, Nilotinib, Oxidative stress, Parkin, Parkinson's disease

Introduction

Parkinson's Disease: Current scenario

Parkinson's disease (PD) was established as a medical condition many years after James Parkinson noted a resemblance in cases amongst his older patients in his 1817 publication "An Essay on the Shaking Palsy" (Shulman et al. 2011). Although it has been proposed that PD emerged as a result of the industrial revolution, there is some evidence that a disease known as "kampavata," consisting of shaking (kampa) and lack of muscular movement (vata), existed in ancient Indian medical system, Ayurveda, as long as 4500 years ago (Manyam, 1990).

The pathology of PD was not well understood until the early 20th century, when the German pathologist Frederick Lewy in 1912 reported neuronal cytoplasmic inclusions in a variety of brain regions. In 1919, Tretiakoff observed that the most critical abnormality in PD was the loss of neurons in the substantia nigra pars compacta of the midbrain. In the 1950s, investigators discovered the importance of dopamine and its depletion from the basal ganglia as the key to understanding the pathophysiology and pathologic biochemistry of PD (Hornykiewicz, 2006).

PD, the second most common neurodegenerative disease affect up to 5% of individuals over the age of 85 (Moghal et al. 1994). The Clinical Symptoms of Parkinson's

*Address for Corresponding Author:
Dr. Vivek Sharma
Asst. Professor
Govt. College of Pharmacy, Rohru, Distt. Shimla-171207
Himachal Pradesh
E mail:viveksharma_pharma@yahoo.co.in
Ph. No. +919816381966

disease are Tremor or shivering, Small Hand Writing, Loss of Smell, Trouble in Sleeping, Trouble moving, Constipation, Soft or low voice, Masked Face, Dizzying or Fainting and Stooping or Hunching over (Tien et al. 2010) and the physical symptoms are neuropathologically correlated with the loss of dopaminergic neurons in the substantia nigra (SN) and deposition of Lewy bodies (LB), cytoplasmic aggregates of the protein α-synuclein (α-syn) in this and other brain regions. The movement disorder arises from reduced dopaminergic input to the striatum as a result of nigral degeneration. Evidence suggests that protein aggregation, mitochondrial dysfunctions, ER stress, neuroinflammation, oxidative stress and reduced growth factor levels contribute to neurodegeneration and play key roles in PD (Gupta et al., 2008; Mullin and Schapira, 2015).

In addition to the physical symptoms, PD patients commonly display non-motor symptoms such as depression, lack of motivation, passivity, and dementia (Fahn, 2003). After PD is diagnosed, patients live an average of 15 years before death occurs (Lees et al., 2009). It is thus of utmost importance to find therapies to counteract the neurodegeneration and restore the neuronal circuits in the brain of PD patients (Lindholm et al., 2016).

It was in 1960s when it was discovered that dopamine present in the striatum is responsible for motor symptoms of PD. Until then, most PD treatments revolved around replacing dopamine, thus ameliorating main pathological features such as slow movement, rigidity and resting tremor. Levodopa was introduced after it was demonstrated that main cause of PD is due to degeneration of dopaminergic neurons of the substantia nigra and for the last several decades Levodopa prescription has been the standard therapy for PD patients although several associated motor complications are observed. Due to the complications associated with levodopa, new drugs in the form of dopamine receptor agonists have been developed for patients who have the early stages of PD; these dopamine receptor agonists confer anti-PD therapy with relatively low risk of developing dyskinesia but they cause more severe non-motor side effects such as mood swings, sleep attacks and fatigue. Therefore, it is concluded that the motor and non-motor side effects in various therapies that use dopamine receptor agonists showed only partial recovery during disease progression and is no longer ideal for anti-parkinsonian therapy. Next breakthrough to treat PD patients came in the form of surgical treatment.

These treatment modalities were based on intervention of basal ganglia circuitry. Initially, surgeries were targeted to internal globus pallidus (GPi) or the subthalamic nucleus (STN) but most recently deep brain stimulation procedures have been adopted to treat PD patients. Although surgical treatment alleviates motor symptoms seen in PD patients, recent studies revealed the side effects of this procedure may lead to non-motor complications that may have occurred due to misplaced DBS electrodes. Dopaminergic cell/tissue grafting has recently been under discussion to treat PD patients but it is minimally effective and can cause unexpected side effects, thus putting this method of treatment in serious doubt. Treating PD patients using stem cells is another lucrative approach; however, due to safety and regulatory issues this approach may not be feasible (Sarkar et al., 2016). These current clinical treatments for PD mainly focus on suppressing disease symptoms, but do not restrict disease progression (Savitt et al., 2006).

Unfortunately, there is no known cure for PD and drugs used to treat it are focused on suppressing symptoms instead of preventing the onset or the progression of the disease. Thus newer targets are continuously identified and searched for and the recent additions to this list of promising disease-modifying compounds in PD include small molecule inhibitors targeting the activity of the c-Abl tyrosine kinase (Hebron et al., 2013).

c-Abl and Tyrosine kinases (Inhibitors)

Kinases are now being considered as an ideal category of drug targets for PD therapy. Research has strongly implicated the dysfunction of kinase activities and phosphorylation pathways in the pathogenesis of PD. Major protein kinases associated with increased risk and cause of PD are PTEN (phosphatase and tensin homolog)-induced putative kinase 1 (PINK1) and leucine-rich repeat kinase 2 (LRRK2). PINK1 and LRRK2-along with their associated protein kinase B (AKT) and c-Jun N-terminal kinase (JNK) are major signaling pathways involved in PD. It is believed that deep evaluation of these signaling pathways will reveal potential therapeutic targets for the attenuation of the cardinal symptoms and motor complications in patients with PD in the future (Mehdi et al., 2016).

c-Abl is the cellular homolog of the Abelson murine leukemia virus oncogene and belongs to the Abl family of tyrosine kinase present in the cytoplasm and nucleus of the cell. In contrast to tumor cells, the activity of c-Abl in post-mitotic neurons is linked to the regulation of the cytoskeleton, to neurite outgrowth, to neuronal plasticity and to the control of cell stress (Schlatterer et al., 2011). Tyrosine kinase inhibitors against c-Abl are neuroprotective and can modulate phosphorylation of specific protein targets in the brain (Dan Lindholm2016). c-Abl is active in sporadic PD leading to parkin tyrosine phosphorylation and accumulation of parkin substrates

suggesting that c-Abl activation could contribute to the degenerative process of PD. Thus, c-Abl inhibitors with brain penetrating properties are attractive disease modifying agents for PD treatment.

c-Abl is expressed in most cells and is part of an intricate network of protein interactions and phosphorylation events in the cell. c-Abl is involved in a variety of physiological functions including the regulation of cell growth and motility, cytoskeleton dynamics, receptor endocytosis, DNA repair, cell survival and autophagy (Hantschel and Superti, 2004). c-Abl is normally present in an inactive form in the cell and its activity is tightly regulated by intramolecular bonds, as well as by binding to protein complexes, and linkage to membranes via an amino terminal myristoyl group. c-Abl is activated following auto-phosphorylation and by the action of other kinases including Lyn and Fyn that are of Src-family.

c-Abl is also activated by DNA damage and during cell stress involving an increased production of reactive oxidative species that ultimately can cause cell degeneration (Hantschel and Superti, 2004). Data from animal models have also shown that c-Abl is activated in brain disorders which are characterized by an increased oxidative stress, including PD (Schlatterer et al., 2011).

c-Abl and the function of this protein is dependent on its subcellular localization. Cytoplasmic c-Abl regulates cellular adhesion and survival pathways, whereas c-Abl in the nucleus or in the mitochondria induces cell cycle arrest and apoptosis upon genotoxic stres (Mahul-Mellier et al., 2014).

cAbl, Nilotinib and PD

c-Abl is a 120 kDa protein belonging to the cytoplasmic tyrosine-kinase family. Similar to the Src kinases, it possesses sequential SH3 and SH2 domains followed by a core catalytic domain with tyrosine-kinase activity (Sirvent et al., 2012). The c-Abl tyrosine kinase is implicated in diverse cellular activities including growth factor signaling, cell adhesion, oxidative stress and DNA damage response. Studies in mouse models have shown that the kinases of the c-Abl family play a role in the development of the central nervous system by affecting neurogenesis, neurite outgrowth and neuronal plasticity (Moresco and Koleske, 2003). It has been demonstrated that c-Abl has a unique myristoylated N-terminal region that negatively regulates its kinase activity (Hantschel and Superti, 2004).

Several studies have shown the involvement of c-Abl in PD using various experimental models (Ko et al., 2010). Studies show that c-Abl protein level is elevated in the postmortem striatum of PD patients (Hebron 2013). The tyrosine kinase c-Abl regulates several cellular processes that may be linked to PD.

The effects of inhibitors of c-Abl activation (phosphorylation) have been studied in animal models of PD. The brain-permeable second-generation c-Abl tyrosine-kinase inhibitor Nilotinib proved effective in a mice model of PD induced by MPTP. MPTP increased c-Abl phosphorylation, decreased dopamine (DA) levels in the striatum as well as the expression of DA transporter (DAT), and decreased the number of TH-positive neurons in the SN. Administration of Nilotinib 7 days before MPTP decreased MPTP-induced phosphorylation, partially restored the the levels of DA, these studies suggest that c-Abl inhibitors can be successfully used for PD.

Nilotinib (Tasigna, Novartis, Switzerland) is a Break point cluster (BCR)- Abl (Abelson) tyrosine kinase inhibitor approved by the U.S. FDA for adults with chronic myeloid leukemia (CML) at oral doses of 600–800 mg daily. Tyrosine kinase inhibitors induce autophagy to destroy rapidly dividing tumor cells in CML. In PD, Nilotinib increases DA levels and improves motor and cognitive outcomes in PD and Alzheimer's disease models. In preclinical studies, Nilotinib enters the brain and inhibits Abl, leading to reduction of oxidative stress and protection of DA neurons. The drug is relatively safe and tolerated but in some patients heart complications have been associated with the use of nilotinib, and therefore a black box warning has been given to the drug by the USA Food and Drug Administration (Lindholm et al., 2016). Compared to the other c-Abl inhibitors, nilotinib is more selective and potent with moderate brain penetration (Soverini et al., 2012).

Targets for Nilotinib in PD

c-Abl is activated in neurodegenerative diseases (Schlatterer et al., 2011) such as Alzheimer's disease (AD), Parkinson's disease (PD) (Ko et al.,2010), Niemann – Pick type C disease (Alvarez et al.,2004) and tauopathies.

Several lines of evidence have suggested that aberrant activation of c-Abl plays important roles in the pathogenesis of PD (i) the c-Abl protein level is upregulated in post- mortem striatum of PD patients and the phosphorylation of c-Abl at Y412 is also enhanced in the substantia nigra and striatum of PD patients (KO et al., 2010; Hebron et al., 2013). Various targets through which cAbl inhibitors may be working are discussed here.

1. PARKIN

Specific mutations in the PARKIN gene are associated with early-onset Parkinson's disease (PD) Oxidative, nitrative or nitrosative stress and dopaminergic stress are thought to impair the function of PARKIN through either covalent modifications and/or alterations in the solubility of PARKIN. The tyrosine phosphorylation of PARKIN by the

oxidative stress-induced non-receptor tyrosine kinase c-Abl has been identified as a regulatory mechanism in PARKIN function. PARKIN is tyrosine phosphorylated in the N-terminal domain by c-Abl, and tyrosine phosphorylation of parkin results in impaired E3-ubiquitin ligase activity and auto-ubiquitination of parkin (Imam et al., 2013).

Among substrates for PARKIN the protein, PARKIN Interacting Substrate (Paris) inhibits the nuclear coactivator PGC-1α that in turn regulates mitochondrial biogenesis and functions (Shin et al., 2011). Inactivation of, or mutations in PARKIN increases levels of Paris and reduce PGC-1α that may lead to mitochondrial dysfunctions and ultimately to neuronal loss (Shin et al., 2011). In contrast expression of PARKIN or PGC-1α can restore these functions and counteract the neurodegeneration (Shin et al., 2011). It was subsequently shown that c-Abl phosphorylates PARKIN reducing its neuroprotective ability, whilst treatment with nilotinib (cAbl inhibitor) increased PARKIN activity (Ko et al., 2010; Dawson and Dawson, 2011; Imam et al., 2011).

c-Abl phosphorylates PARKIN and impairs its E3 ligase activity, leading to loss of dopaminergic neurons in the substantia nigra (KO et al.,2010 Imam et al., 2011). Under pathogenic conditions, where PARKIN is inactivated, PARIS levels increase, which leads to mitochondrial dysfunction through down-regulation of PGC-1a and eventually results in the loss of dopamine neurons that is PARIS-dependent 1 (Karuppagounder et al., 2014).

Heightened c-Abl activity inhibits the PARKIN protein. PARKIN, when acting normally, goes around the cell and tags unnecessary or dysfunctional proteins and mitochondria for degradation. When PARKIN is not working correctly (perhaps because of high c-Abl levels), bad proteins -- such as the key Parkinson's player alpha-synuclein --and damaged mitochondria can build up into toxic clumps and harm the cell. Other cellular players that work with PARKIN (called substrates) also can become toxic to the cell if PARKIN is not functioning correctly. Thus c-Abl-mediated parkin inactivation in response to oxidative and dopaminergic stress seems to be the dominant pathway induced by these stressors.

2. Alpha synuclein and autophagy

Due to abnormal protein folding and ER stress, a toxic protein named Lewy bodies are formed that are commonly observed in PD patients. This toxic protein, Lewy bodies, is made of different proteins such as α-synuclein, synphilin-1 and ubiquitin. Lewy bodies have also been observed in other areas of the brain such as hind brain, spinal cord and enteric nervous system. Lewy bodies first appear in the periphery, subsequently it travels to brain stem and eventually in the cortex (Irizarry et al.,1998; Spillantini et al., 1998).

α-synuclein is a 14 kDa protein that is found in the intraneuronal insoluble fibrillar aggregates called Lewy bodies in PD. α-synuclein is degraded mainly via autophagy including chaperon-mediated autophagy (Cuervo et al., 2004), and overexpression of and modifications/mutations in α-synuclein in

turn, can influence autophagy (Winslow and Rubinsztein, 2011; Klionsky et al., 2016).

Recently it was shown that α-synuclein is phosphorylated by c-Abl at the tyrosine residue 39 that negatively regulates its clearance from the cell (Hebron et al., 2013; Brahmachari et al., 2016). In

contrast, nilotinib enhanced α-synuclein degradation in cultured cells and in animal models of PD. Along with this, c-Abl gene deleted mice have a reduced α-synuclein aggregation and toxicity (Brahmachari et al., 2016). The link between c-Abl and α-synuclein seems reciprocal as the overexpression of α-synuclein can increase c-Abl activity and thereby compromise autophagy (Hebron et al., 2013). Deleting c-Abl from pre-clinical models reduced alpha-synuclein aggregation, while over-expressing c-Abl led to the protein clumps advocationg a direct link between c-Abl and alpha-synuclein, further supporting the role of c-Abl in Parkinson's disease. Thus α-synuclein mediated formation of lewy bodies is also a major target for cAbl inhibitors (Nilotinib).

3. Oxidative stress

Oxidative stress is defined as an imbalance in which the production of reactive oxygen species (ROS) overcomes the antioxidative cell defense system. Oxidative stress can be induced by exogenous and endogenous sources. For instance, hydrogen peroxide and chemotherapeutic reagents are exogenous sources of ROS, whereas mitochondrial energy metabolism is considered a major source for the production of ROS within the cell (Murphy, 2009. ROS can directly react with macromolecules, such as DNA, lipids, and proteins. Oxidative DNA lesions, if unrepaired, can induce mutations and deletions in both nuclear and mitochondrial genomes (Fraga et al., 1990).

ROS signaling is reversible, tightly controlled through a regulatory network. This network results from a concerted assembly of protein complexes, built through protein interactions mediated by interaction modules and posttranslational modifications in the binding partners. Protein modularity and the reversible nature of posttranslational modifications allow the dynamic assembly of local temporary signaling circuits regulated by feedback controls. The strength and the duration of redox signaling are regulated via the oxidative modifications of

the kinases and phosphatases that in turn control the activity of enzymes involved in antioxidant activities and vice versa. Oxidant level modulates c-Abl activity (Sun et al., 2000, Cao et al., 2001).

Oxidative stress activates c-Abl in neuronal cells (Alvarez et al, 2004) and in turn, c-Abl can interact (and regulate) with several enzymes implicated in controlling the redox state of the cell. One of them, the catalase is an immediate effector of the antioxidant cellular defense by converting H_2O_2 to H_2O and O_2 in the peroxisomes. c-Abl and the product of the c-Abl-related gene (Arg) target catalase on the two residues Y321 and Y386 leading to its ubiquitination and to a consequent proteasomal-dependent degradation of the (Cao et al., 2003). Similarly, c- Abl deficient cells display a higher level of expression of the antioxidant protein peroxiredoxin I (Prx1) (Li et al., 2004). Prx1 is considered a physiological inhibitor of c-Abl. Prx1 interacts with the SH3 domain of c-Abl and inhibits its catalytic activity (Wen et al., 1997). Depending on the oxidative level in the cell, glutathione peroxidase1 can be phosphorylated on Tyr-96 and activated by c-Abl/Arg (Cao et al., 2003). In short, c-Abl activation has mostly a negative effect on enzymes involved in the antioxidant defence, with rare exceptions.

Conclusion

Nilotinib is a drug approved for chronic myelogenous leukemia, a cancer of the white blood cells, under the brand name Tasigna. The medication inhibits a class of certain proteins, including one called c-Abl, which is an emerging target for Parkinson's research. In addition to the role of c-Abl in regulating parkin and/or alpha-synuclein, researchers have demonstrated its involvement in dopamine-signaling pathways and oxidative stress too. Too much c-Abl hurts cells by messing with parkin function, inducing oxidative stress, encouraging alpha-synuclein aggregation directly and/or impacting dopamine signaling thus inhibition of cAbl will be beneficial in disorders like PD where these factors has a role to play.

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