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Short Communication

Regeneration Versus Neuroprotection: GDNF Treatment or Targeting the Alpha-Synuclein Pathway in Parkinson's Disease

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Parkinson's disease (PD) represents a prevalent and progressive motor neurodegenerative disorder. The cause of the disease remains obscure, although there are many hypotheses regarding the neurodegenerative processes. The early stages of the illness exhibits marked pathology in the mid-brain, with a characteristic cell loss of at least 60% of the neuromelanin containing neurons in the substantia nigra pars compacta coupled with the presence of the Lewy bodies (LB) in the surviving cells [1]. However, subsequently as the disease progresses the pathology is observed in other areas of the brain and body. The loss of the nigral cell results in a consequential depletion of striatal dopamine levels, which elicits dysfunction and loss motor skills.

There are a host of areas of focus for the treatment of PD including; elevation of the depleted dopamine content in the striatum, or surgery in advanced cases when drugs may be less efficacious, or placements of grafts in areas exhibiting marked pathology, or regeneration of neurons ravaged by the onslaught of the disease process itself, or neuroprotection of the remaining cells from the destructive mechanisms or initiating processes for the removal of toxic species associated with cell destruction.

Nevertheless, the mainstay management of PD is based primarily on symptomatic relief. Levodopa treatment remains the gold standard for PD treatment. It replenishes the low dopamine content in the striatum, resulting in a marked improvement in motor loss or malfunction. However, its long term reduction in efficacy coupled with side effects, have prompted other avenues of management. Hence, exploring regeneration and neuroprotection pathways may offer more sustainable routes for hindering the disease progression.

The objective of regeneration (or restoration) is replacement of lost brain dopaminergic cells. Glial cell line-derived neurotrophic factors (GDNF) support the growth and survival of dopamine neurons.

A Clinical trial study using GDNF [2], involving its infusion directly into the putamen, generated some thought provoking findings. After 18 months of regular GDNF infusions, the parkinsonian patients showed marked elevations of brain dopamine levels compared to controls. Furthermore, there were improvements in "off" time and better "on" time, whereby more "off" periods are reported with the advancing of the disease. In addition, the method of administration (via a port mounted into the skull) appeared to be well tolerated and more importantly the side effects were not severe, although Nutt and colleagues [3] reported paraesthesia and weight loss.

Similarly, administration of GDNF in MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) induced parkinsonism for both young and aged non-human primates exhibited motor improvement [4]. The efficacy of GDNF appears to be attributed more to neuroregeneration of brain dopaminergic neurons rather than protection of the remaining nigral cells [5]. Another important factor to be considered is window of time during which the GDNF is most potent. Parkinsonism induced by administration of neurotoxins in primates, suggest that neuroprotective actions of GDNF is greatest when given soon after the administration of the neurotoxin, so as to prevent subsequent toxin induced nigral cell destruction [4]. Extrapolation of these finding to idiopathic PD, may prove to be challenge. Firstly, it is based on

the assumption that the cause of the illness is induced by a toxin and secondly the absence of a biomarker for the disease. The former is not clear since the cause(s) of PD largely remains unidentified, although there are many hypotheses including the involvement of some neurotoxin. A biomarker would be essential to detect the disease, particularly in the asymptomatic phase and thus administer the GDNF to halt or reduce the progression of the sickness. This may salvage the remaining substantia nigral cells. Neurotrophic factors such as GDNF may delay the development of the illness and thus represent disease modifying treatment.

However, this disease modifying potential may not be effective in the advanced stages of the illness, when fewer nigral neurons remain and the pathology has spread to other areas of the brain. In addition, since GDNF affects the dopamine homeostasis in a dose-dependent manner, therefore the dose of GDNF administered is also central to its efficacy [6]. An alarming feature of the GDNF is that it can induce formation of cancer cells by virtue of its anti-apoptotic effects [7]. This needs to considered carefully, particularly for its long term administration in PD. So, perhaps an alternative could be to protect the remaining substantia nigra neurons from the wrath of the cellular destructive processes.

Neuroprotective agents such as anti-oxidants would be valuable ammunition to the cells against catastrophic events orchestrated by toxic free radical species. Indeed, free radical induced oxidative stress has been closely associated to the mediation of dopaminergic nigral cell loss and degeneration [8]. This notion is endorsed by the reduction of the cellular antioxidant glutathione levels (GSH) in the substantia nigra in incidental Lewy body disease and Parkinson's disease [9]. The presence of Lewy bodies (LB) in the substantia nigra represent, the pathological hallmark of PD, although they are not exclusive to the illness. Their significance to the pathogenesis is further highlighted by their occurrence in the asymptomatic phase of the illness (Incidental Lewy body disease). The misfolded cytosolic protein alpha-synuclein is the perpetrator for the formation of LB.

Chronic gut inflammation and /or oxidative stress have been implicated in the misfolding, oligomerisation and seeding of the protein, alpha-synuclein. This subsequently leads to its aggregation, accumulation and formation of protein inclusion, LB. The periphery has been suggested site for the initial LB production in PD, and subsequently these inclusions are carried via the vagus nerve to the brain. This lethal form of alpha-synuclein rapidly proliferates and affects normal healthy cells too. The close proximity of the appearance of these inclusion and cell death, support the notion that LB plays an integral role in the neurodegeneration cascade.

Interestingly, the native form of alpha-synuclein exerts a protective role in gut by summoning immune cells in response to intestinal infection. In addition, the protein has been associated with synaptic plasticity [10].

From a therapeutic point of view, it would be strategic to prevent the misfolding of alpha-synuclein, which would consequently impede LB formation and possibly slow the progression of the disease. Alternatively, another strategy could be to stimulate the autophagic pathway to reduce the burden of the alpha-synuclein aggregates and thus decrease the formation of LB.

However, the factor(s) that initiate the production of these aggregates are unclear, perhaps there is a genetic involvement. Indeed, mutations in gene GBA 1 observed in Gaucher's disease results in malfunction of the autophagic-lysosomal processes, has been suggested to confer a predisposition for PD [11].

Protein kinases (such as, casein kinase 2) have been associated with alpha-synuclein aggregation via serine 129 phosphorylation. This would represent a putative site for therapeutic intervention, particularly since activation via phosphorylation of tyrosine kinase c-Ab1 triggers apoptotic neuronal cell destruction [12].

A tyrosine kinase c-Ab1 inhibitor, Nilotinib (employed for the treatment of leukaemia) was reported to cross the blood-brain barrier, increase autophagic clearance of alpha-synuclein and attenuate inflammation in the parkinsonian model [13,14]. A clinical study using nilotinib reported promising results [15]. They found motor improvement and an increase in levels of the dopamine metabolite, homovanillic acid. However, these findings need to be interpreted with care since, it was a small group of 12 patients only, also it lacked a pla-

cebo group and the candidates were not standardized. Nevertheless, the potential of nilotinib and for that matter, other tyrosine kinase inhibitors, need to be further explored in larger double-blind clinical trials. Currently, a double blind placebo-controlled Phase IIa clinical trial to investigate the safety and efficacy of nilotinib is being conducted [16,17].

Another line of attack on the neurodegeneration pathway could be, to block the corruption of healthy neurons, thus preserving the remaining cells from the cytotoxic assault of the disease process. This could be achieved by obstructing protein seeding/propagating process. These seeds are agent of transmission of the misfolded alpha-synuclein. This strategy would be beneficial as an augmentation in cell based therapies for PD such as, grafts of human faetal ventral mesencephalon (a source of dopaminergic containing cells). Particularly since, LB pathology has been reported in (11%) of the grafted cells [18].

Nevertheless, to investigate the full potential of any novel cell protection or regeneration treatment, a biomarker would be an imperative tool. Unfortunately, the absence of a biomarker in brain imaging or even present in the blood makes detection of LB in the brain of a living person virtually impossible. Consequently, this diminishes the possibility of halting the disease progression in the early asymptomatic phase (incidental Lewy body disease). This early stage of the illness may be an important point of hindering the degenerative process to salvage the remaining surviving cells and perhaps prevent the occurrence of the symptoms or even manifest a milder form of the disease.

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