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REVIEW

View Point: Disease Modification and Cell Secretome Based Approaches in Parkinson's Disease: Are We on the Right Track?

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Abstract: The term idiopathic Parkinson's disease describes an entity of various not well-characterized disorders resembling each other. They are characterized by chronic neuronal dying originating from various disease mechanisms. They result in the onset of motor and related non-motor features, both of which respond to administration of personalized drug combinations and surgical therapies. The unmet need is beneficial disease course modification with repair and neurogenesis. Objectives are to discuss the value of cell secretome based treatments including neuronal graft transplantation and to suggest as an alternative the stimulation of an endogenous available approach for neuronal repair. Chronic neurodegenerative processes result from different heterogeneous, but complementing metabolic, pathological cascade sequences. Accumulated evidence from experimental research suggested neuron transplantation, stem cell application and cell secretome-based therapies as a promising future treatment with cure as an ultimate goal. To date, clinical testing of disease-modifying treatments has focused on substitution or repair of the remaining dopamine synthesizing neurons following diagnosis. At diagnosis, many of the still surviving and functioning, but already affected neurons have lost most of their axons and are primed for cell death. A more promising therapeutic concept may be the stimulation of an existing, endogenous repair system in the peripheral and central nervous systems. The abundant protein repulsive guidance molecule A blocks restoration and neurogenesis, both of which are mediated via the neogenin receptor. Inhibition of the physiological effects of repulsive guidance molecule A is an endogenous available repair pathway in chronic neurodegeneration. Antagonism of this protein with antibodies or stimulation of the neogenin receptor should be considered as an initial repair step. It is an alternative to cell replacement, stem cell or associated cell secretome concepts.

Keywords: transplantation, dopamine, repulsive guidance molecule A, repair, chronic neurodegeneration, secretome, mesenchymal cells

Plain Language Summary

Experimental research provided extensive insights in the mechanisms of chronic neurodegeneration and developed concepts for new disease-modifying therapies.

Translation of these treatments into clinical practice failed in the heterogeneous disease entity Parkinson's disease with its multiple pathophysiological origins of chronic neuronal dying.

As an alternative, antagonism of the repulsive guidance molecule A pathway is a uniform endogenous available repair and neurogenesis enhancing approach.

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Stimulation of this mechanism should be considered for further future experimental and clinical research on disease modification in Parkinson's disease.

Introduction to Parkinson's Disease

Disease or Disease Entity?

Several lines of evidence suggest that the term "idiopathic Parkinson's disease (PD)" does not reflect one disorder, but a disease entity. Its clinically not well-characterized subtypes resemble each other.[1,2] More than 20 predisposing so-called "PD genes" with a different extent of penetration are currently known. To a certain extent, they are allocated as responsible components for onset of sporadic PD forms. Genetic alterations and mutations in familial PD, such as SNCA, PARK2, LRRK2, DJ-1, PINK-1, UCHL-1, only account for approximately 10% of idiopathic PD patients. Age of onset and clinical symptoms are variable, e.g. convincingly demonstrated in glucocerebrosidase (GBA) mutation carriers.[3–7]

Dopamine Decline: The Common Characteristic

All these PD forms have one feature in common. The essential, neurochemical characteristic is an ongoing progression of dopamine decline due to chronic death of dopamine-generating pigmented neurons in the substantia nigra pars compacta.[2] This small structure is located deep in the core of the human midbrain. Dopamine is mainly synthesized from L-3,4-dihydroxyphenylalanine (Levodopa, L-dopa) after the hydroxylation of tyrosine.

Many Factors Cause the Rising Incidence of PD

Exposure to endogenous and exogenous toxins, such as pesticides or herbicides, paraquat, rotenone, various metals (e.g. iron, manganese, lead), gaseous compounds (such as carbon monoxide) and even viruses is discussed as a contributing factor for the future augmentation of PD cases.[8,9] Generally, frequency of PD goes up with increasing age. Estimates of PD prevalence revealed a 2.4-fold increase in the past 30 years.[10,11] The main reasons are the general rise in human life expectancy, a better public awareness and earlier diagnosis due to better instrumental diagnostic tools, i.e. functional imaging techniques, in combination with enhanced treatment possibilities, which prolong life expectancy with PD.[12] Generally, the further future elevation of PD incidence will elevate the financial burden for health-care systems worldwide.[11]

Principles of Symptomatic Treatment in PD Patients

Considerable research activities in the past 60 years led to the development of therapies to alleviate PD symptoms. The success story of PD treatment was the introduction of the dopamine substitution concept for improvement of motor and to a considerable extent related non-motor symptoms in PD since the 1960s.[13,14] The initial essential breakthrough was the implementation of L-dopa, the blood–brain barrier trespassing metabolic precursor of dopamine, for the treatment of PD. A debate on the use of L-dopa is still ongoing in the scientific community due to the onset of fluctuations of motor behaviour, acceleration of ageing processes and assumptions on L-dopa neurotoxicity.[15,16] Particularly, plasma fluctuations of L-dopa, which are closely associated with dopamine oscillations in the synaptic cleft, counteract the well-accepted concept of "continuous dopaminergic stimulation" for the treatment of PD with its impairment of motor behaviour.[17] There is convincing evidence that continuous stimulation of postsynaptic, nigrostriatal dopamine receptors is an essential precondition for nearly normal movement behaviour in PD patients. In contrast, persistent synaptic dopamine oscillations sooner or later cause onset of so-called motor complications.[17] Their characteristics are changes between adequate motor behaviour, recurrence of motor impairment and involuntary movements, termed as dyskinesia.[17] They are still the focus of current ongoing drug research in PD. Future continuous, subcutaneous L-dopa delivery to the brain by pump devices will improve this still popular issue of motor fluctuations considerably.[18]

The Resurgence of Research on Non-Motor Symptoms and Non-Dopaminergic Neurodegeneration

Clinical researchers have again occupied themselves with non-motor PD symptoms in more recent years. The many years of persisting focus on the dopamine deficiency in PD is now replaced by a more widespread view of altered, heterogeneous neurotransmission in PD patients again. Since the 1950s, it is known that an individual different, heterogeneous decline of neurotransmitters, such as serotonin (5-HT), norepinephrine etc., occurs in PD.[19,20] The current resurgence of research on non-dopaminergic changes in PD also again discusses the importance of microglial activation and neuroinflammation as disease

mechanisms.[21–24] Both of them may hypothetically initiate the disease process, but may also occur as secondary, concomitant phenomena of chronic neurodegeneration. To date, extensive experimental and neuropathological research have provided distinct and better insights and understanding of chronic neuronal and associated glial cell death in the past fifty years. The predominant responsible, final mechanism cascades are now well identified.[25]

Disease Modification in PD is Not Available Yet

Based on the extensive knowledge on processes of neuronal dying, antiapoptotic, neuroprotective or oxidative stress reducing compounds, were successfully tested in experimental PD models.[26–32] To date, these therapeutic approaches were more or less not successful in clinical trials with PD patients and accordingly they were not approved as a disease-modifying treatment in PD (e.g.[33]). Even studies on neuron transplantation or application of neuronal growth factors did not provide convincing benefits (important studies:[34,35]).

Objectives

Thus to date, the unmet needs are beneficial disease course modification and cure in PD. The objectives of this review are to discuss cell secretome-based therapeutic approaches including neuronal graft transplantation in PD and to describe a more uniform therapeutic approach for repair as an initial treatment step. A systematic literature search was not performed, as this article is a viewpoint.

Cure or Disease Modification by Dopamine Generating Cell Transplants?

Current available dopamine substituting treatment strategies only temporarily and dose-dependently improve the heterogeneous symptom complex characterized by motor and associated non-motor features during the chronic neurodegenerative process in PD patients.[36]

Transplants of Dopamine Synthesizing Cells

Replacement of dopamine-generating neurons in the striatum with fetal grafts or human embryonic stem cells was believed to provide symptomatic benefits and to help sparing of dopamine substitution dosing.[37] Human, fetal ventral mesencephalon tissue was grafted as a source of dopamine-generating cells into PD patients. Clinical benefits were observed to a certain extent. Postmortem investigations demonstrated integration of these cells in the brain network and their subsequent long-term survival.[38] The high incidence of graft-induced dyskinesia was attributed to the presence of 5-HT synthesizing neurons within the transplant. It may hypothetically also result from an uncontrolled dopamine synthesis by the transplants, which independently act and are not adapted to existing brain regulation systems of physiologic neurotransmission.[39–41] A further drawback was the observed host-to-graft transfer of PD with uptake of host-derived α-synuclein followed by a subsequent aggregation in Lewy bodies.[39,42–45] Generally, enrichment of misfolded α-synuclein in Lewy bodies is looked upon as one of the main responsible and important, neuronal, pathological phenomena in PD. It is well known, that failures within physiological activities of protein metabolism initiate protein degradation and -misfolding. These abnormalities are discussed as a PD specific process and are looked upon as responsible for PD onset and progression.[46] However this pathological protein accumulation may also be the result of an unspecific side reaction of the metabolic cascade during chronic neurodegenerative processes. It may hypothetically only represent well-wrapped protein waste as a consequence of physiological defence mechanisms.[46]

Drawbacks of Tissue Grafting

The therapeutic value of grafting with fetal neuronal tissue in PD may additionally face ethical restrictions due to limited tissue supply.[39,42–44] Embryonic porcine ventral mesencephalic tissue, autologous carotid body cells, respectively adrenal medullary tissue and even human retinal pigmentary epithelial cells were also considered.[34,43,44] Availability, storage and self-renewal of cell sources appeared to be easier. Laboratory findings were successful in the case of immunological compatibility between the donor cells and the host.[47] One has to consider, that different major histocompatibility complex antigens, respectively human leukocyte antigens, may counteract successful transplant integration. When not matched and no immunosuppressant drugs are applied, the transplant will be deemed foreign by the host and rejected by the adaptive human system. It initiates an immune response to remove foreign pathogens.[48] In the case of CNS transplants, this reaction is more or less fatal. Thus graft rejection is still a major unresolved issue in the

field and limits the successful translation into clinical use, i.e. in PD patients.[49]

Transplantation - A Promising Therapeutic Tool in the Real World?

However, the transplantation sooner or later of dopamine-generating cells as a replacement strategy faces some problems from the view of clinicians. At the time of PD diagnosis, 50–70% of dopamine-generating neurons in the nigrostriatal system are already gone. One hopes that regenerative therapy will stimulate the differentiation of new cells for the replacement of the ones that are already dead. Reactivation of cells, that are still viable but dysfunctional or in a dormant phase, is also promising. Protection with attenuation of the inflammatory processes, or stimulation of repair systems may be suitable therapeutic mechanisms.[21–23,50,51] Replacement by transplantation will focus on dopamine-generating neurons only. Amelioration of motor symptoms is the focus. However, PD also affects other neurotransmitter systems and causes onset of a wide array of vegetative and non-motor features.[52] PD is heterogeneous in terms of course and expression of symptoms. There are considerable doubts, whether this disease entity follows a fixed pattern of progression.[2,52–56] Nowadays, new therapies are mainly experimentally established in uniform disease models in the laboratory. They aim on specific cell types only. Therefore the translational process will face serious problems due to the heterogeneity of PD patients.[1,57,58] Accordingly, transplantation of dopamine-synthesizing cells provided benefits. They resemble the effects provided by a continuous L-dopa delivery, i.e. with the future available subcutaneous L-dopa infusion with a pump device.[18] This approach or other currently applied dopamine substitution concepts allow a dosing adaptation to the ongoing neurodegenerative process. This is in contrast to transplantation. Sooner or later the grafts even shared α-synuclein enrichment. Moreover, necessary repeat adaptation to the probably further ongoing, rather heterogeneous, neurodegenerative process in the long term is complex.[34,39,42,43,45,53] Thus in the end, the market and the acceptance by PD patients will decide, whether a simple future reversible treatment procedure, such as the subcutaneous L-dopa infusion with a to-be-developed simple device technique similar to insulin application in diabetes, will be favored by patients and payers compared with grafting treatment concepts. Accordingly, both therapies do not encounter the existing unmet need of cure or disease modification in PD in contrast to application of mesenchymal cells, respectively their products.

Stem Cells and Cell Secretome Based Therapies

Mesenchymal stem cells have a certain potential to serve as a valid therapeutic option with engraftment and subsequent differentiation capacity.[59,60] They also deliver bioactive molecules. They are generally referred to as "the secretome".[61] It consists of proteins, such as cytokines, chemokines, and growth factors, lipids.[62,63] Their functions are to promote cell survival and differentiation, prevent neuronal cell death, protect other cells from oxidative stress or regulate inflammatory processes.[61,62,64] They improved motor impairment in animal models of PD, which mainly reflect the characteristics akinesia, rigidity and tremor and abnormal movement sequences, such as dyskinesia, to a certain extent.[59,61,64,65]

Cell Secretome

The use of secretome per se is easier compared with conventional stem-cell based techniques and applications.[57] Manufacturing, storage and handling is easy. They are ready-to-use biological products. They do not require additional suppression of the immune system by adjuvant therapies.[66–68] Therapeutic change to cell-specific effects is possible. Problems such as immune compatibility or induction of tumours, and respectively infection transmission are less.[66,69] The secretome aims on disease modification.[59,61,62,65] It may solve multiple regulation procedures of key biological processes. Thus it enables neuroprotection, neurodifferentiation or neuroinflammation.[22,23] As an example, the secretome may enhance release of brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor or neurotrophin 3.[59,61,62,65] These neurotrophins are essential for protection and survival of dopamine-generating neurons. This was shown in experiments in animal models of PD induced by e.g. 6-hydroxydopamine- or rotenone exposure.[61,62,65–68,70]

Exosomes

Exosomes are bioactive molecules, which are released by mesenchymal stem cells.[63] Exosomes are nano-sized extracellular vesicles and can be used as carriers of other therapeutic modalities. They only weakly stimulate defence by immune system activities. They avoid

clearance by the reticuloendothelial system. They cross the blood–brain barrier due to their small size.[61,62,65,67,68] Exosome exposure was shown as an efficacious mode of action following direct mesenchymal stem cell transplantation. Their beneficial therapeutic effects reduced loss of dopamine neurons with concomitant amelioration of the motor deficits in the 6-hydroxydopamine PD animal model.[71–74]

Conclusion

Experimental findings repeatedly offer promising and exciting future therapeutic opportunities, which were successfully tested in the laboratory. To date, none of the aforementioned therapies for PD modification or cure survived the translational process into clinical useful treatments for PD patients, and have not yet been approved. The unmet need for cure, disease modification, repair or regeneration still exists in PD. The list of past clinical trial failures is long.

Possible Causes for Failures

One simple reason is that chronic neurodegenerative processes result from different heterogeneous, but complementing metabolic, pathological cascades (fundamental findings:[15,75,76]; reviews:[77,78]). They end up in neuronal cell death-inducing events. They are well characterized. A typical example is apoptosis, which is the suicidal cell programme.[25,79] However, the processes which initiate onset of PD or are responsible for the progress of chronic neuronal dying, probably vary in PD and have a multifactorial origin. Neuronal death in PD causes an individually pronounced and variable expression of motor and non-motor symptoms. Specific, individual different personality features, socioeconomic factors, such as education, etc., influence the acceptance, expression, adaptation and compensation of clinical deficits in PD patients. All these components complicate the translational process from bench to bedside. The term "neuroplasticity" is used as explaining the phenomenon of the differing capacity to compensate deleterious metabolic processes and to delay symptom onset.[80] This heterogeneity in PD, even in more rare genetic PD forms, interferes with the value of assessment tools in clinical trials. High numbers of study participants may not counteract these dilution factors of possible positive effects resulting from a therapeutic disease-modifying intervention. To demonstrate the benefit of disease modification, validated clinical rating scales were used in the past, sometimes even in combination with functional imaging techniques, e.g. visualization of the dopamine neurotransmission in PD (as example:[81]). However, it is well known that rating scores are biased by examiners and by symptomatic drug effects, e.g. L-dopa or dopamine agonists.

The Importance of Early, Premotor Diagnosis

There is consensus that an essential precondition for PD course modification is an early diagnosis, at a time when the damage resulting from PD is low. Biomarkers or identification of a genetic predisposition for PD may be excellent screening instruments for "prodromal" PD diagnosis or PD-at risk-individuals before the onset of motor symptoms. To date, PD is diagnosed relatively late in the disease process. There are estimates that 60% of dopaminergic axons and 30% of nigral dopaminergic neurons are already gone, when motor symptoms appear.[50] Thus in the clinical trials, testing of a disease-modifying therapy takes place with a focus on the remaining 70% dopamine synthesizing neurons in the most affected nigrostriatal area. Many of these still surviving and functioning, but already affected neurons have already lost most of their axons. They are primed for cell death. At this stage, a more promising therapeutic concept may be the stimulation of an existing, endogenous repair system in the peripheral and central nervous system.[51,82–86]

An Underestimated Concept: Stimulation of Repair?

Antagonism of the repulsive guidance molecule A (RGMa) pathway is worth more widespread consideration. It may serve as initial step for repair both in experimental and clinical research on disease modification in PD.

The RGMa Pathway and PD

Several lines of evidence suggest that RGMa is involved in PD pathophysiology. A RGMa protein increase in the substantia nigra was found following *in situ* hybridization and immunohistochemistry in neuromelanin positive neurons of post-mortem brain tissue, taken from L-dopa-treated PD patients.[83] In view of the ongoing discussion on L-dopa neurotoxicity, one cannot exclude that this outcome may also be associated or at least aggravated by L-dopa administration and the L-dopa exposure associated oxidative stress generation.[15,87] Evidence accumulates that RGMa, when

located outside of cells, inhibits regeneration of axons and is involved in the acceleration of neuronal demise.[88–90] Therefore inhibition of the RGMa pathway with antibodies or antagonism of the neogenin receptor activity, may initiate regenerative repair in the peripheral and central nervous system. In PD, an appropriate time will be after the diagnosis. It shall be an initial step to slow or stop progression of the ongoing disease process and to induce neuronal and glial repair.[80,91–94] In view of the multifactorial pathophysiological events, which initiate the disease process in PD, this approach is a more general and thus uniform one.

Current Ongoing Disease Modifying Interventions in PD

Specific trials based on e.g. genetic findings, as for instance the currently tested concept convincingly demonstrated in GBA mutation carriers, are or will be soon be under way in clinical studies.[3–7] Similar ones are the current ongoing trials with antibodies against misfolded proteins based on the corresponding neuropathological findings.[29,95] Various drug mechanisms are discussed to reduce misfolded α-synuclein and thus disease progression. The focuses are boosting of autophagic/lysosomal clearance, reduction of α-synuclein mRNA by modulating histone deacetylase or RNA interference with decreased expression of α-synuclein.[96] Other concepts aim on the impeding of the α-synuclein multimerization with heat shock proteins, dissociation of existing misfolded α-synuclein aggregates with small molecules, blocking of α-synuclein entry through receptor blocking, prevention of α-synuclein transport from cell to cell and immunotherapy with extracellular or intracellular neutralization.[97] All these innovative approaches have one, essential, disadvantage. They are based on a more or less singular molecular pathology derived from a neuropathological postmortem finding. Clinical trials, which investigate an α-synuclein antibody, such as BIIB054, were already performed. They reported the pharmacokinetics, safety and tolerability in phase I, prasinezumab did not show relevant clinical benefits according to MDS-UPDRS outcomes.[98–101]

Inhibition of RGMa: The Future Concept?

In contrast RGMa antagonism considers the existing metabolic similarities both in the peripheral and central nervous system, as it was effective in other nervous system disorders according to experimental findings.[51,86,89,102,103] Thus lowering of physiological RGMa effects restores neuronal function in the long term as a more general working concept for repair (Figure 1). It even weakens effects of toxin exposure.[80,83,84,91,92,104–106] Currently, two different neutralizing RGMa antibodies (ABT-555 [elezanumab]; MT-3921) are investigated in phase 2 clinical trials in spinal cord injury. In addition ABT-555 is tested in phase 2 clinical trials in progressive and relapse-remitting multiple sclerosis and in ischaemic stroke. Positive results of these clinical studies will support the use of this repair strategy in the chronically damaged human nervous system, like in PD. Transplantation and cell secretome research in PD also aim on neurogenesis. It is worth mentioning, that inhibition of neurogenesis is performed by the RGMa-neogenin pathway, which probably also occurs in PD.[51,82,86,107] Neurogenesis also takes place in the adult human brain, in the dentate gyrus or the subventricular zone. RGMa has been shown to block neurogenesis in these areas.[89,108] One may postulate that aiming on RGMa function with antibodies may even stimulate neurogenesis in the adult human brain of PD patients. Thus elevation of neurogenesis may also improve motor and non-motor features in PD and beneficially influence the further course of PD. To date it is far from clear, how frequently and long this RGMa pathway

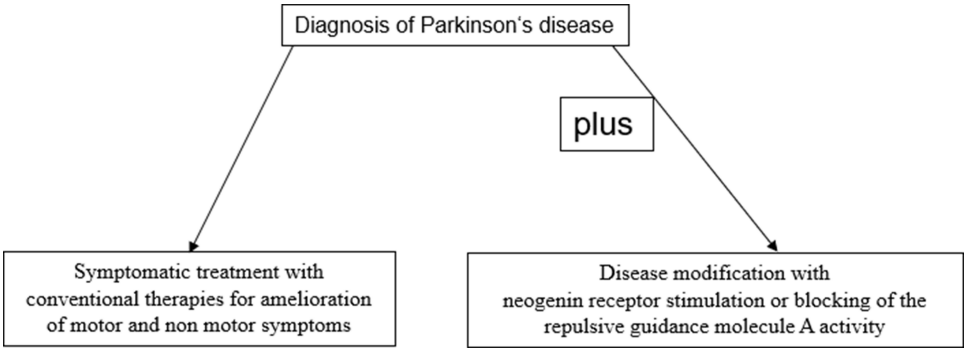

Figure 1 Concept for disease modification in Parkinson's disease with repulsive guidance molecule A pathway modulation.

modulating therapy has to be repeated in the further course of PD. Further experimental and then clinical research is warranted to test this approach. The future will be a combination of treatment of symptoms and repair following diagnosis (Figure 1). Negative long-term consequences are not known. More detailed pharmacokinetic investigations in humans are needed.

Conclusion

RGMa antagonism is an alternative, more simple approach to cell replacement, stem cell and/or associated cell secretome concepts. It does not aim on specific cell types or disease mechanisms, since it represents a more uniform approach for the various disease mechanisms in chronic neurodegeneration, including the disease entity PD.[1,81,109–114]

Disclosure

The authors report no conflicts of interest in this work.

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