Relationship between Apolipoprotein Superfamily and Parkinson's Disease

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Abstract

Objective: Parkinson's disease (PD) is featured with motor disorder and nonmotor manifestations including psychological symptoms, autonomic nervous system dysfunction, and paresthesia, which results in great inconvenience to the patients' life. The apolipoprotein (Apo) superfamily, as a group of potentially modifiable biomarkers in clinical practice, is of increasing significance in the diagnosis, evaluation, and prognosis of PD. The present review summarized the current understanding and emerging findings of the relationship between Apo superfamily and PD.

Data Sources: All literatures were identified by systematically searching PubMed, Embase, and Cochrane electronic databases with terms "Parkinson disease," "apolipoprotein," and their synonyms until May 2017.

Study Selection: We have thoroughly examined titles and abstracts of all the literatures that met our search strategy and the full text if the research is identified or not so definite. Reference lists of retrieved articles were also scrutinized for additional relevant studies.

Results: The levels of plasma ApoA1 are inversely correlated with the risk of PD and the lower levels of ApoA1 trend toward association with poorer motor performance. Higher ApoD expression in neurons represents more puissant protection against PD, which is critical in delaying the neurodegeneration process of PD. It is suggested that *APOE* alleles are related to development and progression of cognitive decline and age of PD onset, but conclusions are not completely identical, which may be attributed to different ApoE isoforms. *APOJ* gene expressions are upregulated in PD patients and it is possible that high ApoJ level is an indicator of PD dementia and correlates with specific phenotypic variations in PD.

Conclusions: The Apo superfamily has been proved to be closely involved in the initiation, progression, and prognosis of PD. Apos and their genes are of great value in predicting the susceptibility of PD and hopeful to become the target of medical intervention to prevent the onset of PD or slow down the progress. Therefore, further large-scale studies are warranted to elucidate the precise mechanisms of Apos in PD.

Key words: Apolipoprotein A1; Apolipoprotein D; Apolipoprotein E; Apolipoprotein J; Parkinson's Disease

Introduction

Parkinson's disease (PD) is a complex progressive neurodegenerative disorder and the second leading cause of neurodegeneration with an estimated prevalence of about 1% of individuals older than 60 years[1] and 2% of the population older than 65 years.[2] Motor dysfunction is the typical manifestation of PD, including resting tremor, rigidity, bradykinesia, and postural instability. However, nonmotor features of PD, such as cognitive function decline, depression, neuropsychiatric symptoms, and autonomic features, have drawn a great attention recently.[3,4] Currently, the diagnosis by assessing the clinical extrapyramidal signs (tremor, rigidity, bradykinesia, and postural instability) is relatively late in the pathological process when approximately 70% of dopaminergic neurons have degenerated[5,6] and 50% of dopaminergic neurons have lost in the substantia nigra,[7] as well as that dopamine levels in the striatum are 80–85% depleted,[8] and it will be far too late to be altered by potentially neuroprotective treatments at the point of clinical diagnosis. PD symptoms resemble other

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neurodegenerative disorders leading to an estimated clinical diagnostic accuracy ranging between 75% and 90%.[9] Previous studies have made great efforts to search for clinical biomarkers (e.g., haptoglobin, transthyretin, complement factor H, fibrinogen, thrombin, glutathione S-transferase-Pi, and urine)[10-12] that can be applied to identify the individuals in the early stage of PD, evaluate the progression status, assess the effect of clinical intervention, and predict the disease prognosis. Nevertheless, none of them have been verified rigorously to indicate PD at the onset of disease or be related to the disease severity. Recently, some studies have found that apolipoprotein E (ApoE), ApoA1, ApoD, and ApoJ play important roles in the initiation, progression, and prognosis of PD.[10,12-15]

Apos function as structural protein components of lipoproteins, including six types: A, B, C, D, E, and J. Most of them are synthesized in liver and partially in small intestine. Apos are of critical importance in lipid transportation and metabolism, which can stable the structures of lipoproteins, activate or suppress lipoprotein metabolism enzymes, and guide the plasma lipoproteins to receptors on cell surface when they are integrated with plasma lipids. Apos are closely related to the onset of atherosclerosis, diabetes, hyperlipoproteinemia, and cardiovascular disease, with different types and pathogeneses. Human cerebrospinal fluid (CSF) Apos are distinct from their plasma counterparts in type or subtype, concentration, size, and location. Expressions of Apos were observed in oligodendrocytes, astrocytes, and perivascular cells,[16,17] and the emergence in the central nervous system (CNS) was also confirmed. Apos were shown to be related to nerve damage,[18] and their aggregation was detected after injury,[19] as well as in elderly brain and degenerative disorders.[20,21] The present review will describe the current knowledge and emerging findings in relationship between lipocalin superfamily and PD so as to update the diagnosis and medical intervention of PD.

APOLIPOPROTEIN SUPERFAMILY

Apolipoprotein A1

ApoA1, a single polypeptide chain consisting of 243 amino acids, is the major structural protein of high-density lipoprotein (HDL). ApoA1 can activate lecithin cholesterol acyltransferase, and it is closely involved in suppressing inflammatory reaction, protecting vascular endothelium, and regulating immune response. ApoA1 passes through the blood–brain barrier by transcytosis from plasma instead of being synthesized by brain neurons. In addition, it is expressed as a protective factor in atherosclerosis and Alzheimer's disease (AD) in many studies. Recently, ApoA1 has been considered as a correlate of age at onset and motor severity in PD. The receiver operating characteristic curves for plasma ApoA1 as a PD marker versus control classifier (71% sensitivity and 60% specificity) are comparable with those described for CSF α-synuclein (71% sensitivity and 53% specificity), arguably one of the most mature diagnostic biochemical biomarkers at present in PD.[22] Some studies have demonstrated that ApoA1 level in plasma is remarkably lower in PD compared to normal neurological status, even after adjusting for age, sex, and other confounding factors.[23-26] Lower ApoA1 level is associated with earlier age at onset of PD,[27,28] indicating that ApoA1 may be a neuroprotective factor for dopaminergic system integrity. Two recent large epidemiological studies reported that the risk of PD decreased in individuals who took statin medications,[29,30] which was attributed to the increasing levels of ApoA1 and HDL caused by statins. Plasma ApoA1 level was reported to be genetically influenced by *APOA1* gene (rs670) with a single nucleotide polymorphism at position − 75 bp in the gene promoter, and the allele of rs670 was reported to be related to higher plasma ApoA1 and HDL levels.[26] ApoA1 has been found at altered levels and oxidatively damaged in PD, as well as other neurodegenerative disorders, resulting in malfunction of cholesterol processing, dysregulation of inflammatory response, and acceleration of neurodegeneration.[31] This could be ascribed to the concept that the oxidized ApoA1 loses the ability to inhibit the tumor necrosis factor-s release and therefore leads to neuronal death consequently.[31] ApoA1 may take part in delaying the dopaminergic neurodegeneration, promoting the repair of damaged neurons, and maintaining the integrity of the neurons with anti-inflammatory and antioxidant properties. Unfortunately, the definitive pathogenesis is still unclear.

It was revealed that the plasma ApoA1 level was correlated with age of PD onset and also associated with the progress of disease and severity of motor impairment.[27,32] A meta-analysis with more than 1000 PD patients conducted by Swanson *et al*.[27] found that plasma ApoA1 level was highly connected with the severity of motor impairment in PD patients, and the lower plasma ApoA1 level was linked with poorer performance on the motor section assessed by the Unified Parkinson Disease Rating Scale. ApoA1 has been identified as a new and potentially modifiable candidate biomarker of PD risk, and it is indicated that ApoA1 is related to the anti-oxidative and anti-inflammatory enzyme paraoxonase 1 (PON1), a major anti-atherosclerotic component of HDL, and lower ApoA1 level is associated with decreased activity of PON1.[28] In turn, it increases the formation from low-density lipoprotein to 27-hydroxycholesterol, an oxidized cholesterol metabolite that could increase α-synuclein level and cause apoptosis,[28] which results in neuronal death finally. In addition, Ikeda *et al*.[33] have also reported that PON1 activity levels decline in PD patients compared to controls. It is possible that higher ApoA1 level may delay the neurodegeneration processing of PD through PON1-related mechanism. A significant association was found between plasma ApoA1 and putaminal dopamine transporter (DAT) uptake, and it was also confirmed that lower ApoA1 level was related with more severe DAT deficit, even adjusting the confounding factor.[31] Hence, the level of ApoA1 could possibly reflect the severity of motor impairment based on the concept that the level of DAT uptake could reflect motor impairment extent. It has been suggested that increasing ApoA1 plasma

levels by small amounts might have a profound impact on decreasing the incidence of PD,[28] and the levels of ApoA1 could be influenced by potential drugs (e.g., statin) or lifestyle changes.

All the researches mentioned above have indicated that ApoA1 may act as a protective biomarker and medical target in PD. Therefore, large-scale prospective studies are extremely warranted to identify the precise role of ApoA1 in PD and explore the underlying pathophysiological mechanism.

Apolipoprotein D

ApoD, a 29-kDa glycoprotein that belongs to lipocalin superfamily, is presented in the majority of corporal fluids (breast cyst fluid, lachrymal secretions, apocrine axillary's secretions, CSF, urine, and component of HDLs)[34] as well as a wide variety of different organs and tissues (e.g., spleen, testes, and brain) in mammals. ApoD could act as a carrier of arachidonic acid (AA) and hydrophobic molecules, and is confirmed to be mainly expressed by fibroblasts in mammalian tissues.[35,36] In peripheral nervous system, ApoD is synthesized by endoneurial fibroblasts and found with an elevated level during degeneration, whereas ApoD expressions are observed in neurons, oligodendrocytes, astrocytes, and perivascular cells in CNS, and it is manifested that the ApoD level increases during development, aging, degeneration, and regeneration processes.[35,37-42] For instance, increasing levels of ApoD have been observed in CNS affected by AD, Niemann-Pick disease, schizophrenia, and PD,[13,42-44] which is consistent with the conclusion that ApoD might have an important role in binding, transporting cholesterol, and maintaining cholesterol homeostasis during reinnervation and regeneration.

Oxidative stress is believed to be involved in the development of neurodegenerative disorders, and glutathione (GSH) depletion in substantia nigra is thought to play an important role in the pathogenesis and progression of PD. It has been reported that limiting AA release and metabolism may provide benefits in PD patients,[45] and it can be explained that metabolism of AA could result in the generation of oxygen-free radicals and contribute to cellular damage and death in the condition with an existing depletion of GSH. AA can be converted into many biologically active compounds that serve as potent messengers in regulating the inflammatory response and inducing neurotoxicity during the degeneration of dopaminergic neurons.[46] Therefore, inhibiting AA metabolism can protect neurons from oxidative toxicity in the condition of GSH depletion.[47] It was implicated that ApoD might be a neuroprotective molecule in PD on account of the fact that ApoD could prevent AA release by stabilizing membrane-associated AA and chaperoning-free AA in the cell.[48] A recent study conducted by Ordoñez et al.[13] revealed that the dopaminergic neurons of substantia nigra lacked immunostaining for ApoD in both PD and control groups, whereas glial cells surrounding neurons showed the immunoreactive response for ApoD and increasing signal in PD cases. This has indicated that

nigral dopaminergic neurons are not able to express or assemble ApoD, and therefore they are unable to protect themselves properly and more vulnerable to stressors. The increasing ApoD level in the surrounding glial cells was considered to be the source of neurotrophic factors and could protect neurons against neurotoxicity induced by oxidative stressors.[49] In accordance with the findings above, a homolog of ApoD has been observed in the fruit fly as a protective role in stress situations, and it is suggested that the lifespan will decrease and neurodegeneration will accelerate if a scarcity of ApoD exists.[50]

In summary, ApoD is instrumental in stabilizing cell homeostasis and plays an important role in neuronal protection. Higher ApoD level may halt or slow down the neurodegeneration process of PD through binding and transporting molecules that can generate neurotoxicity to dopaminergic neurons. It seems that upregulating the level of ApoD in substantia nigral neurons through pharmacological agents or other practicable methods can be a promising medical treatment for PD patients.

Apolipoprotein E

ApoE is a crucial element in the lipoprotein metabolism,[51] lipid transportation,[52] and clearance of amyloid proteins in brain.[53] APOE gene locates on the chromosome 19q13.2 with 3 alleles (e2, e3, and e4) and 6 genotypes (E2E2, E2E3, E2E4, E3E3, E3E4, and E4E4).[54] In addition, the e3 allele is the most common with a frequency of approximately 70–80%[55] and considered as the normal allele, whereas the e2 and e4 alleles are formed as results of a single amino acid substitution at position 112 (rs429358) or 158 (rs7412).[56]

ApoE is mainly synthesized by astrocytes in the CNS and associated with cerebrovascular diseases[57] as well as neurodegenerative disorders, such as late onset of AD.[58,59] Significant similarities in pathogenesis are indicated between PD and AD development, which are both characterized with neuronal loss and protein aggregation. Recently, ApoE has become a significant biomarker for investigating the susceptibility of PD and PD dementia (PDD), and it is considered as an indicator of cognitive decline in PD and AD patients. Some studies showed that the e2 allele was associated with higher risk of PD.[60,61] A meta-analysis including 22 studies has highlighted that the presence of APOE2 allele is linked with increased susceptibility for PD,[62] which is accordant with the conclusion of another meta-analysis.[63] It was suggested that the e4 allele was responsible for PD development,[61,64-67] while others concluded that both the e2 and e4 alleles enhanced the susceptibility of PD.[61,63,65,68-73] As mentioned above, the results were inconsistent, and many studies did not detect significant difference in APOE allele frequencies between PD patients and controls.[2,74-78] Two previous meta-analyses and a latest one involving 8546 PD patients and 10,403 healthy controls implicated that there was no remarkable association between APOE polymorphism and the incidence of PD. Therefore, no assured agreement of the relationships between APOE alleles and PD risk has been reached.

Genetic risk factors and multiple environmental elements are determinants in the etiology and pathogenesis of PD. The inconsistencies between studies may be explained by differences in patients' characteristics including ethnic background, age of PD onset, time of diagnosis, and disease severity. Methodologies that are used to detect the levels of ApoE isoforms also have influenced the results of studies, and it is believed that environmental factors are greatly involved in the neurodegeneration process of PD, which may conceal the actual relationships between *APOE* alleles and the incidence of PD. Previous studies should be interpreted cautiously on account of relatively small sample size.

PDD accounts for 22–48% of all the PD individuals; 75% of PD patients who have lived more than 10 years after diagnosis[79] and 80% over the course of PD.[80] The underlying mechanisms are not fully comprehended; however, it seems that Lewy body targeting the cingulate and posterior association areas is involved in the dementia process,[81] and widespread cholinergic deficits in brain cortical regions were presented as the loss of dopaminergic neurons in PDD.[82] Genotype of *APOE* is the most extensively studied potential genetic risk factor for dementia in PDD.[10] Some cross-sectional studies evaluated the effect of the *APOE* genotype on dementia[14,61,66,73,83-86] and concluded that *APOE* gene expression might be correlated with the development of cognitive decline of PD. A large-scale meta-analysis with 1145 cases and 501 controls suggested that the overrepresentation of *APOE*-ε4 carriers was present in PDD patients compared to controls,[63] which was consistent with the other meta-analysis that consisted of 458 pooled PD cases (163 with dementia and 295 without).[67] More rapid cognitive decline was discovered in PD patients with *APOE*-ε4 carriers than noncarriers in the longitudinal study performed by Morley *et al*.[87] over 4 years. Nevertheless, the *APOE* genotype did not show any relevance to PDD in several studies.[61,88-91] It has been found that there is no association between *APOE* genotype and the development of dementia in a community-based longitudinal cohort study with 107 newly diagnosed PD patients (Cambridge, UK) followed up for an average of 5 years[63] and another cohort research (*n* = 64) followed up for an average of 9.7 years.[89] Possible explanations for failing to find the correlation between *APOE* genotype and cognitive status are summarized as follows: (1) It is difficult to verify the underlying relationship between *APOE* genotype and PD development that studies are featured with small sample size, insensitive measures of identifying dementia, and missing data during follow-up; (2) PD patients are somehow under the protection of *APOE* gene variation (polymorphism) through possible mechanisms that are not yet clear;[87] (3) The contribution of *APOE* genotype to the cognitive status in PDD is not identical like the specific pathways of Lewy body disease, or the effect that *APOE* exerts on Alzheimer's cognitive status.[14]

Previous researches not only investigated the influence of ApoE on PD or PDD, but also tried to reveal the correlation between ApoE and psychosis. Psychosis, which is manifested with hallucinations, delusions, and impaired insight, is shown to be an independent risk factor for developing dementia and increasing nursing home placements and mortality in PD patients.[92,93] The research including 424 PD patients suggested that *APOE* carrier of PD patients was linked with the increasing odds of hallucinations within the first 5 years after diagnosis.[66] Higher occurrence of visual hallucinations has been discovered in *APOE* carrier during the course of disease,[94] which indicates that *APOE* genotype could possibly be applied to identify patients who are at risk of psychosis and formulate therapies to prevent or treat psychotic symptoms in PD. However, some other studies could not replicate the same results.[66,75,95-97] The conflicting results among studies may be ascribed to racial differences of populations and the lack of uniform inclusion criteria for PD patients with psychosis.

It is widely acknowledged that *APOE* allele carriers are more likely to develop AD; however, the influences that *APOE* genotypes exert on PD are not exactly the same. The discrepancies might be due to the different ApoE isoforms' impacts on both disorders.[1] It has been found that statins could induce neuroprotective effects by lowering serum ApoE levels in neurodegenerative diseases, such as PD.[98] Therefore, prospective longitudinal studies are warranted to demonstrate the relationships between *APOE* alleles and PD progression.

Apolipoprotein J

ApoJ (also known as clusterin, CLU, SGP-2, SP-40, and gp80), a highly conserved heterodimeric glycoprotein, has been observed to participate in a number of biological processes, such as lipid transportation, cell adhesion, complement-mediated cell lysis, and programmed cell death.[99] *APOJ* gene expression was upregulated in many severely disturbed physiological statuses and neurodegenerative diseases, such as PD, dementia with Lewy bodies, multiple system atrophy, and AD.[100] It is believed that β-amyloid (Aβ) peptides are critical part in the progression of neurodegeneration, and clusterin has been shown to be involved in the signaling pathway that Aβ exerts its neurotoxic effects to neurons.[101] It is demonstrated that Aβ peptides rapidly target the clusterin protein and their complexes are responsible for pathological changes subsequently, which suggests that blocking the effect of Aβ on clustering is likely to be a novel approach to halt disease progression.[101]

It has been suggested that ApoJ can prevent α-synuclein aggregation by colocalizing with α-synuclein in Lewy bodies as a molecule chaperone.[102] An association, independent of *APOE* genotype and known risk factors of PD, was revealed between clusterin-specific single-nucleotide polymorphism (rs11136000) and PD. It was indicated that cortical Lewy body pathology or concomitant AD pathology somehow was involved in the PD development.[103] Significantly higher CSF clusterin level was implicated in histologically verified PD patients compared to controls

and those with disease duration under 2 years, which probably reflects the fact that most neurodegenerative changes in PD patients occur in the initial stage of disease.[99] Furthermore, another study published recently also found the same phenomenon that higher clusterin CSF levels were shown in PD and PDD patients versus controls,[104] and the increasing levels of clusterin were observed in both plasma and CSF in PD patients by unbiased quantitative proteomic techniques.[12] A recent study conducted by van Dijk *et al.*[105] concluded that clusterin levels were not correlated with the disease duration, stage, and severity of motor symptoms. The discrepancy between van Dijk *et al.*'s study and that of others' may be attributed to the disparities of patient characteristics and technical variations of assays. Furthermore, those conflicting results may also be ascribed to the presence of diversities of pathological and clinical conditions, which can conceal the real correlation between ApoJ and PD when PD patients are compared with neurologically healthy controls, such as a tension headache, vertebrogenic disease, psychogenic disease, migraine, and diabetic neuropathy in brain tissue[99,105] due to the increasing (not decreased) levels of clusterin in those situations.[106]

In spite of the absence of correlation between clusterin level and PD in van Dijk *et al.*'s study,[105] positive correlations between clusterin levels and AD-related proteins (Aβ-42, T-tau, and P-tau) were observed, which could be explained by that clusterin might have a direct effect on their metabolism.[107] In addition, CSF T-tau has been coming up as a potential biomarker of the severity of neuronal degeneration in PD.[108] The present results do not exclude the possibility that higher clusterin level might be an indicator of later cognitive decline or correlated with specific phenotypic variations in PD.[105] The association between higher clusterin level and PD is stronger in patients with dementia than without, which is consistent with the conclusion that the clusterin level is correlated with cognitive decline in AD. Increasing the expression of clusterin will probably be a promising therapeutic approach of PD if the association of ApoJ and PD can be verified by future researches.[109] Fortunately, clusterin gene-based therapies did show beneficial effects in treating atherosclerosis and peripheral neuropathies in animals,[110] and the effectiveness was found in AD as well.[111]

Conclusion

Apo superfamily is closely associated with dopaminergic system integrity and disease severity in PD patients. Apos are of great prospect to be biomarkers with capabilities of identifying patients in early stage, evaluating the disease severity, and providing viable treatments. The underlying mechanisms involved are still needed to be authenticated in the near future; therefore, large quantities of studies are warranted.

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