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Proposal and Point of View on Targeting α-synuclein for the Treatment of Parkinson's Disease

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Opinion Article

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ABSTRACT

Many scientific studies in the biochemical, genetic fields suggest that there were common mechanisms, such as genes, α-synuclein protein, tau protein, oxidative stress, mitochondrial dysfunction, and iron might be shared in Alzheimer disease (AD) and Parkinson disease (PD). α-synuclein is suggested to have a vital role in the pathogenesis of PD and is a promising therapeutic target. However, gap might always exist between clinical and basic researches. The failure of recent phase III trials of the anti-Amyloid-β (Aβ) monoclonal for AD prompts us to rethink PD therapy strategies. As multiple mechanisms are involved in PD pathogenesis and their relative roles might vary at different stages of this disease. Use of comprehensive prevention strategies and targets at different stages of PD might be a promising way to cure or prevent PD in the future.

Keywords: Alzheimer disease; Parkinson disease; α-synuclein; neurodegeneration; amyloid-β.

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1. SOME COMMON MECHANISMS MIGHT BE SHARED IN ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE

Alzheimer disease (AD) and Parkinson disease (PD) are both neurodegenerative diseases, whose symptoms and pathological changes overlap each other in their late phase. Whether there are common genetic risks, as well as the existence of linkage disequilibrium, epigenetics and other mechanisms between AD and PD is still controversial. It needs large-scale genome-wide association studies (GWAS) of different mutual authentication in the future. In terms of mechanism, AD and PD all belong abnormal protein folding diseases. Previous paper in Science reported that Amyloid-β (Aβ) of AD and α-synuclein of PD as well as other abnormally folded proteins had the same spatial conformation. Many mechanisms such as genes, α-synuclein protein, tau protein, oxidative stress, mitochondrial dysfunction, iron, and locus coeruleus, involved in AD and PD may be the same. There were common mechanisms, which might be shared in AD and PD, were supported by many scientific studies in the biochemical, genetic, and molecular fields [1]. It is presumed that AD and PD might have a common upstream pathogenic pathway.

2. α-synuclein PROVIDES US WITH HOPE AND CONFIDENCE FOR THE TREATMENT OF PD

α-synuclein is a 140 amino acid neuronal protein that has been associated with several neurodegenerative diseases. Many mutations in the gene coding for the α-synuclein protein have been identified in familial and sporadic PD since the first mutation has been found in a rare familial form of PD. α-synuclein were discovered to be predominantly component of the aggregated proteinaceous inclusions called Lewy body (LB) found in PD and cortical Lewy body dementia (LBD). Aberrant aggregation of α-synuclein has been detected in an increasing number of neurodegenerative diseases, collectively known as synucleopathies. α-synuclein exists physiologically in both soluble and membrane-bound states, in unstructured and α-helical conformations, respectively.

It is well known that LB is the characteristic pathological sign of PD, and fibrous aggregates of α-synuclein are the main elements of LB. As the same core of Aβ in AD, the position and roles of α-synuclein in the etiology of PD are not easy to be shaken. A subsequent series of cell culture and animal experiments had confirmed the affirmative role of α-synuclein in the pathogenesis of PD [2]. Many academics had suggested that therapeutic strategies might target on α-synuclein for the treatment of PD, which indicate that α-synuclein appears to be a very promising targets for PD. It has also been discovered that duplication or triplication of the wild type α-synuclein gene itself can lead to a familial form of PD [3-5]. This evidence suggests that overexpression of the normal, wild type α-synuclein protein itself can lead to the development of PD. α-synuclein might lie in the upstream of PD pathological process, which mainly exists as three kinds of monomers, oligomers, and polymer [6]. Wakabayashi found that mainly toxic effects come from soluble oligomers, which suggests that α-synuclein oligomers may be a key factor in the pathogenesis of PD. Many studies have shown that α-synuclein forming LB may have dual effects. The formation of LB is thought to have a protective effect (Proctective sinks), which is conducive to α-synuclein oligomers fibrosis and thus reducing its toxicity effect, preventing nerve cells from erosion due to α-synuclein toxicity. With the increasing of α-synuclein aggregation, the aggregated α-synuclein might exhibit prion-like effect, which can adopt a self-propagating conformation that causes neurodegeneration. Recent evidence now suggests the possibility that α-synuclein is a prion-like protein and that PD is a prion-like disease. α-synuclein in an aberrantly folded, β-sheet-rich form could migrate from affected to unaffected neurons [7]. Laboratory studies also confirm that α-synuclein can transfer from affected to unaffected nerve cells, where it appears that the misfolded protein can serve as a template to promote host α-synuclein misfolding. Immunization therapy with human α-synuclein could reduce α-synuclein aggregate formation and attenuate neurodegeneration in human α-synuclein transgenic mice [8]. A subsequent series of experiments in vivo and vitro suggested that antibodies against α-synuclein reduce cell-to-cell transfer of the protein by directing extracellular α-synuclein to microglia [9].

3. GAP MIGHT ALWAYS EXIST BETWEEN CLINICAL AND BASIC RESEARCHES

However, the clinical practice tells us that there often exists far distance between the basis

pathogenesis and clinical outcomes of the disease. There is not always concordant between them. So that the results coming from basic and clinical research often appear to be different, even contradictory. Just as a prerequisite for evidence-based medicine, medicine-based evidence is always in overwhelming status in clinical practice. However, sometimes there exists the paradox between evidence-base medicines with practice-base evidence. For example, Aβ is suggested to have a vital role in the pathogenesis of AD and is a major therapeutic target. Recently, phase III trials of two monoclonal antibodies against Aβ, bapineuzumab and solanezumab, failed to significantly improve clinical outcomes in patients with mild to moderate AD [10,11].

4. RETHINKING THE STRATEGIES OF PD THERAPY

Overproduction and clearance disabilities of α-synuclein become an important cause of PD pathogenesis. Therefore, there is no doubt to target on α-synuclein for the treatment of PD. However, just like the pathology of AD, once PD pathological process started, subsequent pathological reactions would gradually increase, forming a vicious cycle of their own, which includes: increasing the permeability of the lipid bilayer, destroying the integrity of the synaptic vesicles, interfering dopamine metabolism, and axoplasmic and vesicles transportation of intracellular substances from the endoplasmic reticulum to the golgi, mitochondria damage, inhibiting the proteasome activity, molecular chaperone mediated autophagy and histone acetylation, leading to proteasome degradation resistance, causing hyperphosphorylation of tau protein, oxidative stress and neuroinflammation [12]. Most patients diagnosed with PD in clinical practice have been in the middle or late stage of the disease. If only targeting on α-synuclein for the treatment of PD, it is difficult to obtain an ideal effect. Therefore, early diagnosis is crucial to PD treatment. The further studies on the prevention and treatment for PD should focus on the following points: Firstly, aiming at PD high-risk population screening and early diagnosis of PD, finding out method and the strategy for detection of PD high-risk groups and patients in the premotor phase of PD, on the base of which, the PD diagnosis standard might be revised in the future. The development of PD can be regarded as a continuous evolution process consisting of the preclinical stage or asymptomatic stage (including the pre-physiological phase), premotor phase, the early motor symptoms (the pre-diagnostic phase) and motor symptoms stage (the diagnostic phase).

Research shows that the brain has begun to appear relevant pathological damage before motor symptoms of PD appear [13]. How to predict and diagnose PD in preclinical stages of PD without symptoms is an important prerequisite for early prevention of PD. Second, for patients in the middle and late stage, comprehensive treatment strategies aiming at more aspects of this disease is needed. Except for blocking the core pathological processes of PD, it should be endeavor to reconstruct the functional balance of the neurotransmitter control loop in the brain of PD patients based on existing pathology that is called "rebuilding a new home on the ruins." Third, we should actively explore effective exercise rehabilitation therapies such as occupational therapy, physical therapy, and Tai Chi style motortherapy. These are perhaps wonderful strategies which could improve the life quality of patients in the middle and late stage. From the perspective of PD prevention, it can be mainly targeted on α-synuclein production and clearance. While once the onset of PD occurs, from the perspective of therapy, multiple therapeutic targets for comprehensive treatment are needed. It is afraid that a single target treatment is difficult to achieve the desired results.

Inflammation is a common pathological process of various diseases, which are also involved in the development and progression of PD [14]. Previous studies showed that chronic inflammation in the body including α-synuclein production and tau protein hyperphosphorylation could promote the occurrence and the development of PD. PD pathological process will promote intensify of inflammatory response, including production of inflammatory mediators and activation of glial cells. Inflammation and α-synuclein could form a vicious circle, promoting and intensifying each other. Suppression of the nervous system inflammatory response would contribute to cut off α-synuclein-inflammation vicious cycle. Recently, researchers have found that autoimmune mechanisms are involved in the pathogenesis of PD [15,16], which suggests that the generalized inflammation is indispensable for the PD pathogenesis process. Previous study has found that nonsteroidal anti-inflammatory drugs (NSAID) for the treatment of PD have a certain significance [17,18]. Therefore, as one of the comprehensive treatment strategies of PD,

anti-inflammation should be necessary and promising.

5. LOOKING FORWARD THE PD THERAPY STRATEGIES

How to successfully cure PD? The current evidence suggests that anti-α-synuclein therapies, as a preventative measure, should be given in the early stage of the disease. Being different from Aβ to AD, α-synuclein has not yet been discovered. There exist a dynamic equilibrium conditions in the central and peripheral system. Researchers found that the plasma levels of α-synuclein were low in normal subjects and patients with PD [19]. There seemed not necessarily link between plasma levels of α-synuclein with disease onset in PD patients. Therefore, not like AD, we could not reach the purpose of the central α-synuclein removal by eliminating the peripheral α-synuclein. However, studies have found that exogenous α-synuclein is most likely to be aggregated in the plasma of PD patients. It seems to imply that there might have some factors which could promote α-synuclein overproduction and aggregation in the internal environment of PD. Therefore, for the prevention and treatment of PD, on the one hand, we should not just only focus on the clearance of α-synuclein, most important of all, promote to explore and discover the root cause which results in α-synuclein overproduction and aggregation, thereby eliminating its upstream precipitating factor.

There is a need to find out new therapeutic strategies that not only provide symptomatic relief but also reverse the neuronal damage hampering PD progression. To prevent oxidative stress or reduce mitochondrial dysfunction might contribute to PD treatment [20]. One of the promising therapeutic targets for potential disease-modifying treatment of Parkinson's disease (PD) is leucine-rich repeat kinase 2 (LRRK2) [21]. Successful therapeutic management might be obtained by targeting pathogenesis of PD at different disease stages. This method should effectively prevent the production of α-synuclein, protection of synaptic function and inhibition of α-synuclein hyperphosphorylation at the preclinical stage; removal of aggregated α-synuclein, protection of synaptic function and neurons, and attenuation of α-synuclein hyperphosphorylation at premotor phase of PD; rebuilding the functional balance of the neurotransmitter control loop in the brain of PD, that is called, "rebuilding a new home on the ruins" at the early stage of motor symptoms. Comprehensive prevention strategies should be adopted, such as targeting α-synuclein accumulation, synaptic dysfunction, α-synuclein hyperphosphorylation, synaptic function disorder, neuroinflammation and oxidative stress, especially focusing on neuroprotection, effective exercise rehabilitation and cognitive training, which cloud contribute to improve movement disorders and cognitive dysfunction of PD, especially gait disorder and as well as their quality of life at motor symptoms stage.

6. CONCLUSION

As multiple mechanisms are involved in PD pathogenesis and their relative roles might vary at different stages of this disease. Use of comprehensive prevention strategies and targets at different stages of PD might be a promising way to cure or prevent PD in the future.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Xie A, Gao J, Xu L, Meng D. Shared mechanisms of neurodegeneration in Alzheimer's disease and Parkinson's disease. Biomed Res Int. 2014;648740.
2. Al-Mansoori KM1, Hasan MY, Al-Hayani A, El-Agnaf OM. The role of α-synuclein in neurodegenerative diseases: From molecular pathways in disease to therapeutic approaches. Curr Alzheimer Res. 2013;10:5595-68.
3. Chartier-Harlin MC, Kachergus J, Roumier C, Mouroux V, Douay X, Lincoln S, Levecque C, Larvor L, Andrieux J, Hulihan M, Waucquier N, Defebvre L, Amouyel P, Farrer M, Destée A. Alpha-synuclein locus duplication as a cause of familial Parkinson's disease. Lancet. 2004;364: 1167-1169.
4. Ibanez P, Bonnet AM, Debarges B, Lohmann E, Tison F, Pollak P, Agid Y, Dürr A, Brice A. Causal relation between alpha-synuclein gene duplication and

familial Parkinson's disease. Lancet. 2004; 364:1169-1171.
5. Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna T, Dutra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson MR, Muenter M, Baptista M, Miller D, Blancato J, Hardy J, Gwinn-Hardy K. alpha-Synuclein locus triplication causes Parkinson's disease. Science. 2003;302:841.
6. Bosco DA1, Fowler DM, Zhang Q, Nieva J, Powers ET, Wentworth P Jr, Lerner RA, Kelly JW. Elevated levels of oxidized cholesterol metabolites in Lewy body disease brains accelerate alpha-synuclein fibrilization. Nat Chem Biol. 2006;2:249-253.
7. Olanow CW, Brundin P. Parkinson's disease and alpha synuclein: Is Parkinson's disease a prion-like disorder? Mov Disord. 2013;28:31-40.
8. Masliah E, Rockenstein E, Adame A, Alford M, Crews L, Hashimoto M, Seubert P, Lee M, Goldstein J, Chilcote T, Games D, Schenk D. Effects of alpha-synuclein immunization in a mouse model of Parkinson's disease. Neuron. 2005;46:857-868.
9. Bae EJ, Lee HJ, Rockenstein E, Ho DH, Park EB, Yang NY, Desplats P, Masliah E, Lee SJ. Antibody-aided clearance of extracellular α-synuclein prevents cell-to-cell aggregate transmission. J Neurosci. 2012;32:13454-13469.
10. Salloway S, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med. 2014; 370:322-333.
11. Doody RS, et al. Phase 3 trials of solanezumab for mild–to–moderate Alzheimer's disease. N Engl J Med. 2014;370:311-321.
12. Bennett MC. The role of alpha-synuclein in neurodegenerative diseases. Pharmacol Ther. 2005;105(3):311-331.
13. Postuma RB, Montplaisir J. Predicting Parkinson's disease-why, when, and how? Parkinsonism Relat Disord. 2009; 15(Suppl 3):S105-109.
14. Deleidi M, Gasser T. The role of inflammation in sporadic and familial Parkinson's disease. Cell Mol Life Sci. 2013;70:4259-4273.
15. Benkler MG, Agmon-Levin N, Shoenfeld Y. Parkinson's disease, autoimmunity, and olfaction. Int J Neurosci. 2009;119:2133-2143.
16. Benkler M, Agmon-Levin N, Hassin-Baer S, Cohen OS, Ortega-Hernandez OD, Levy A, Moscavitch SD, Szyper-Kravitz M, Damianovich M, Blank M, Chapman J, Shoenfeld Y. Immunology, autoimmunity, and autoantibodies in Parkinson's disease. Clin Rev Allergy Immunol. 2012;42:164-171.
17. Gao XA, Chen HL, Schwarzschild MA, Ascherio A. Use of ibuprofen and risk of Parkinson disease. Neurology. 2011;76: 863.
18. Gagne JJ, Power MC. Anti-inflammatory drugs and risk of Parkinson disease: A meta-analysis. Neurology. 2010;74:995-1002.
19. Besong-Agbo D, Wolf E, Jessen F, Oechsner M, Hametner E, Poewe W, Reindl M, Oertel WH, Noelker C, Bacher M, Dodel R. Naturally occurring α-synuclein autoantibody levels are lower in patients with Parkinson disease. Neurology. 2013; 80:169-175.
20. Filograna R, Beltramini M, Bubacco L, Bisaglia M. Anti-oxidants in Parkinson's disease therapy: A critical point of view. Curr Neuropharmacol; 2015. [Epub ahead of print]
21. Taymans JM, Greggio E.LRRK2 Kinase inhibition as a therapeutic strategy for Parkinson's disease, where do we stand? Curr Neuropharmacol; 2015. [Epub ahead of print]

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