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α -Synuclein, Synphilin and E3 Ubiquitin-Ligase (SIAH and Parkin): The Key to Understanding Parkinson's Disease

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ABSTRACT

Parkinson's disease (PD) is one of the most common neurodegenerative disorders characterized by the progressive loss of dopaminergic neurons in the substantia nigra. Following the loss of dopaminergic neurons is the accumulation of the inclusion bodies commonly referred to as Lewy bodies that contain α -synuclein, synphilin, SIAH and parkin. These are small proteins that have special relevance for understanding PD. Not only are α -synuclein, synphilin, SIAH and parkin found in Lewy bodies characteristic of PD, but also mutations in the gene for α -synuclein, synphilin, SIAH or parkin can cause an inherited form of PD and over-expression of normal α -synuclein or synphilin is thought to increase the risk of developing PD in sporadic or non-familial cases. However, the mechanisms involved in the death of dopaminergic neurons as well as the role of Lewy bodies in the pathogenesis of the PD are still unclear. Parkin and SIAH are E3 ubiquitin-ligases that ubiquitylate themselves and promote their own degradation. Parkin and SIAH interact with polyubiquitylate synphilin (the α -synuclein interacting protein) and in the same manner monoubiquitylate α -synuclein. Taken together, formation of Lewy bodies occurs upon coexpression of α -synuclein, synphilin, SIAH and parkin. This review discusses the way and manner in which the interaction of α -synuclein, synphilin, SIAH and parkin has been thought to be responsible for developing PD.

Keywords: α -synuclein, synphilin, SIAH, parkin, Lewy bodies, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is one of the most common neurodegenerative disorders characterized by four cardinal features: rigidity, bradykinesia, tremor and postural instability, and affects nearly 1% of people over the age of 65 [1,2]. Histopathological features include loss of dopaminergic neurons, notably in the substantia nigra pars compacta, with a concomitant accumulation of inclusion bodies variously known as Lewy bodies [3,4]. Other than associated with a single gene mutation, more than 95% of PD cases are sporadic in nature, in some cases epidemiologically linked to pesticide exposure [5,6]. Both sporadic and inherited forms of PD are characterized by substantial loss of dopaminergic neurons, predominantly in the substantia nigra that are the target of most current symptomatic therapies [7].

α -synuclein, synphilin, SIAH and parkin are small proteins that have special relevance for understanding PD [7,8,9]. Not only are α -synuclein, synphilin, SIAH and parkin found in Lewy bodies characteristic of PD, but also mutations in the gene for α -synuclein, synphilin, SIAH or parkin can cause an inherited form of PD and over-expression of normal α -synuclein or synphilin can increase the risk of developing PD in sporadic, or non-familial, cases [7,8]. However, the mechanisms involve in the death of dopaminergic neurons as well as the role of Lewy bodies in the pathogenesis of the PD are fully understood [7]. Thus, it is thought that α -synuclein, synphilin, SIAH and parkin, especially in their mutant forms or under conditions where their expression levels are dramatically

increased, are toxic proteins such that they are associated with an increased rate of neuronal cell death [8,9]. This review discusses the way and manner in which the interaction of α -synuclein, synphilin, SIAH and parkin has been thought to be responsible for developing PD.

α -Synuclein

α -synuclein is first member of the family proteins it belongs to and predominantly found in both synapses and nuclei bound to lipids and is associated with presynaptic vesicles in the neurons, and thus the name α -synuclein [7]. In humans, there are three synuclein family members (α -, β -, γ -) and all synuclein genes are relatively well conserved both within and between species [7,10]. The synuclein genes are specific to the vertebrate lineage such that neither single cell organisms (including yeast) nor invertebrates (*Drosophila melanogaster*, *Caenorhabditis elegans*) have any apparent synuclein homologue [7]. Moreover, primate α -synuclein sequences differ from other vertebrate synucleins by a substitution of Alanine for a Threonine at position 53 [7,11]. Although the normal function of α -synuclein is poorly understood, it is thought to be markedly expressed in the brain; most notably within neurons and to a lesser extent found in other tissues, e.g., hematopoietic cells [7,12].

Interestingly, a key elucidation to understanding PD was thought to be an A53T mutation in the α -synuclein gene, i.e., a reversion of the human Alanine to the ancestral Threonine found in rodents and many other species; which was the genesis for dominantly familial disease [7,13]. Equally, this has been the first clear-cut evidence that a Mendelian gene might be responsible for causing PD, which to some extent was found to be sporadic in nature [7]. Since then, two other point mutations namely: A30P and E46K have been reported in different families [7,14,15]. In summary, three different point mutations in the gene encoding for α -synuclein, as well as gene locus triplication were found to cause some rare familial cases of PD [7].

Furthermore, α -synuclein has been the major component part of Lewy bodies in sporadic forms of PD that is monoubiquitylated by E3 ubiquitin-ligase such as SIAH and parkin; and in the same manner interacts with synphilin, which colocalizes with α -synuclein leading to formation of Lewy bodies and neurodegeneration [7,8]. The accumulated, histopathological forms of α -synuclein aggregates were found to show lower solubility than that of the normal protein [7,9]. This might have been due partly to post-translational modification such as truncation, S-nitrosylation, ubiquitylation and phosphorylation [7]. Therefore, α -synuclein deposition into Lewy bodies could be a marker of the PD disease state.

Synphilin

Synphilin is an α -synuclein interacting protein that in humans is often encoded by the *SNCAIP* gene. *SNCAIP* stands for "synuclein, alpha interacting protein" and this gene encodes a protein containing several protein-protein interaction domains, including ankyrin-like repeats, a coiled-coil domain, and an ATP/GTP-binding motif [16]. Like α -synuclein, synphilin is a presynaptic protein that associates with synaptic vesicles [8]. Synphilin-1 has previously been characterized as a protein that interacts with α -synuclein and leads to the formation of Lewy bodies upon cotransfected with the non-A β component (NAC) portion of α -synuclein in cultured cells [8]. Two forms of synphilin have so far been identified namely synphilin-1 and its novel isoform called synphilin-1A. In contrast, synphilin-1A lacks exons 3 and 4 found in synphilin-1, and displays an extra exon (termed 9A) located between exons 9 and 10 [17]. Synphilin-1A is by far more neurotoxic and aggregation-prone protein than that of synphilin-1 [17,18]. Equally, alternatively spliced transcript variants encoding different isoforms of this gene have been demonstrated, but their full-length nature is still under investigation [16].

The encoded protein of either synphilin-1 or synphilin-1A interacts with α -synuclein in neuronal tissue and each one of them is polyubiquitylated both in vitro and in vivo by SIAH and parkin, and consequently leading to formation of Lewy bodies [8,17,18]. Additionally, a mutation associated with synphilin-1 gene comes from the finding which identified two sporadic PD patients with the same point mutation (R621C) in synphilin-1 [8]. The R621C mutation reduces the ability of synphilin-1 to form inclusion bodies and this might have been due partly to inability of synphilin-1 to colocalize with α -synuclein [17]. Thus, synphilin is an intrinsic component of Lewy bodies in PD [8].

Seven In Absentia Homolog (SIAH)

SIAH is an E3 ubiquitin-ligase that interacts with ubiquitylates α -synuclein and synphilin and is present in Lewy bodies of PD patients. Like parkin, both SIAH-1 and SIAH-2 are RING finger domain E3 ubiquitin-ligase. The nature of ubiquitylation of synphilin by SIAH is polyubiquitylation, in contrast to α -synuclein which is monoubiquitylation [8,18]. In humans, there are two highly conserved forms of SIAH namely SIAH-1 and SIAH-2, but significantly differ in their N-terminal region before their RING-finger domain and are markedly expressed in the central nervous system, as well as other tissues [19]. However, the interaction and monoubiquitylation of α -synuclein by SIAH-2 is much stronger when compared with SIAH-1 and monoubiquitylated α -synuclein is not targeted for degradation by the proteasome system [8,20]. In agreement with this, the monoubiquitylation of α -

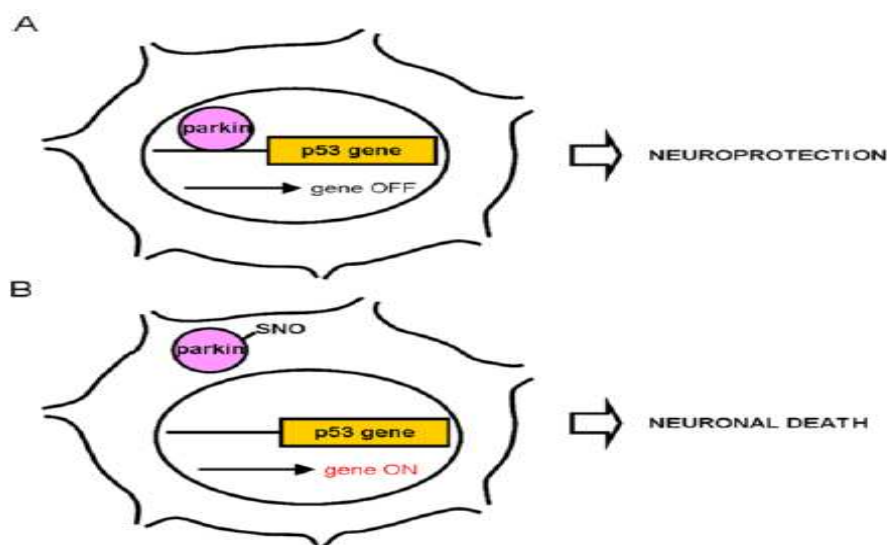
synuclein by SIAH-2 so far identified was not accompanied by degradation [8].

In addition, SIAH promotes limited polyubiquitylation of synphilin-1A that does not lead to its degradation by the proteasome [18]. SIAH also increases the formation of synphilin-1A inclusions in the presence of proteasome inhibitors, supporting the participation of ubiquitylated synphilin-1A in the formation of Lewy body [18]. It has been reported recently that the E3 ubiquitin-ligases SIAH-1 and SIAH-2 interact with polyubiquitylate synphilin-1, promoting its degradation through the ubiquitin proteasome system [8].

Parkin

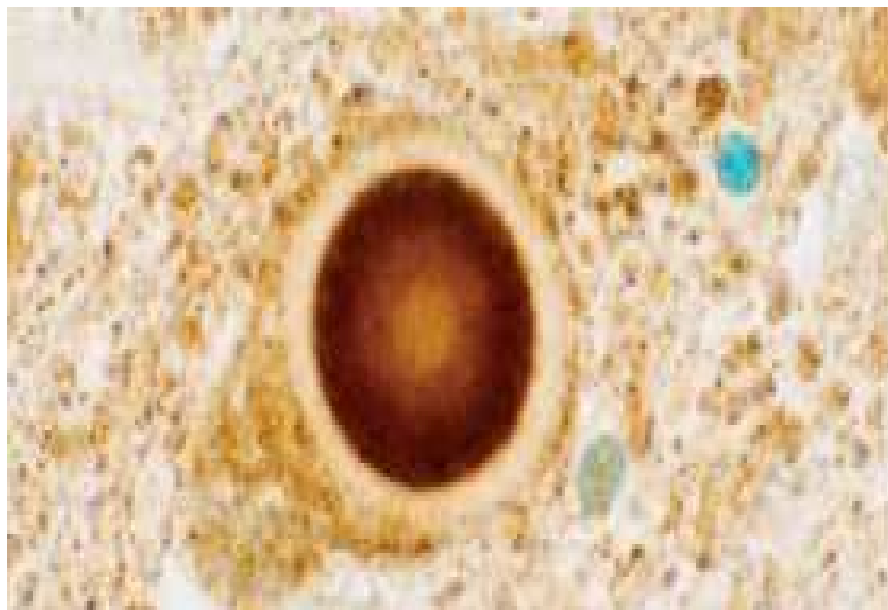
Parkin is an E3 ubiquitin-ligase which in humans is encoded by the *PARK2* gene [21]. It was found to interact with polyubiquitylate, monoubiquitylate synphilin and α -synuclein respectively and in the same manner is a component part of Lewy bodies [8,9]. This is because patients with parkin mutations (*PARK2*) do not have Lewy bodies in the surviving dopaminergic neurons [21].

Parkin was also reported to ubiquitylate a glycosylated form of α -synuclein, but does not act on unmodified α -synuclein and monoubiquitylated α -synuclein is not targeted for degradation by the proteasome system [20,22]. Additionally, mutations in this gene are known to cause a familial form of PD known as autosomal recessive juvenile Parkinson's disease (AR-JP) [21]. This form of genetic mutation is thought to be one of the most common known genetic causes of early-onset PD [23]. In one study of patients with onset of PD prior to age 40 (10% of all PD patients), 18% had parkin mutations, with 5% homozygous mutations [23]. Such patients develop a syndrome that closely resembles the sporadic form of PD; however, they tend to develop symptoms at a much younger age [21]. Although other neuroprotective functions of parkin as a novel transcriptional repressor of p53 have been recently demonstrated, how the loss of function of the parkin protein leads to dopaminergic cell death in this disease is not fully understood [9]. The prevailing hypothesis is that parkin helps degrade one or more proteins toxic to dopaminergic neurons [21].



Lewy Bodies

Lewy bodies are abnormal aggregates of proteins that often develop inside nerve cells in PD, and Lewy body dementia [8,24]. They are identified under the microscope when histology is performed on the brain and appear as spherical masses that displace other cell components [24]. The two morphological types are classical (brain stem) Lewy bodies and cortical Lewy bodies. A classical Lewy body is an eosinophilic cytoplasmic inclusion consisting of a dense core surrounded by a halo of 10-nm-wide radiating fibrils, the primary structural component of which is α -synuclein followed by synphilin, SIAH and parkin. In contrast, a cortical Lewy body is less well defined and lacks the halo [8,24]. Nonetheless, it is still made up of α -synuclein fibrils. Cortical Lewy bodies are a distinguishing feature of dementia with Lewy bodies (DLB), but may occasionally be seen in ballooned neurons characteristic of Pick's disease and corticobasal degeneration, as well as in patients with other tauopathies [24]. They are also seen in cases of multiple system atrophy, particularly the Parkinsonian variant [25].



Lewy body

CONCLUSION

It is not surprising that loss of dopaminergic neurons and the accumulation of Lewy bodies are the significant part of the pathogenesis of PD. Although the extent of apoptosis of dopaminergic neurons with respect to accumulation of Lewy bodies needs to be established, the prime suspect for neurodegeneration has currently been thought to be the interaction of synphilin-1A with associated α -synuclein and synphilin-1. Equally, the ubiquitylation of α -synuclein, synphilin-1 and synphilin-1A suggested the participation of E3 ubiquitin-ligase such as SIAH and parkin in the pathogenesis of PD.

Recommendations

Since proteasomal dysfunction has been implicated in the pathogenesis of PD, post-translational modifications such as S-nitrosylation, ubiquitylation and phosphorylation of α -synuclein, synphilin-1, synphilin-1A, SIAH and parkin should be carefully evaluated because these pathways afford golden opportunity for developing novel therapeutics for PD especially NOS inhibitor.

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