The role of viruses in the pathogenesis of Parkinson's disease

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Parkinson's disease (PD) is a neurological degenerative disorder characterized by loss of dopaminergic neurons in the substantia nigra (SN) and intracellular inclusions called Lewy bodies and Lewy tangles, composed mainly by aggregates of α-synuclein. Braak et al. (2003) proposed that the olfactory epithelium and intestines are the anatomical sites where PD initiates; as pathological aggregates of α-synuclein are detected in these tissues in very early or prodromal PD. In this scenario, α-synuclein seems to reach the central nervous system (CNS) by axonal transport through the sympathetic nervous system, the glossopharyngeal and vagus nerves as well as the olfactory pathways (Braak et al., 2003).

Currently a large amount of information on how α-synuclein propagates within the nervous system has been accumulated. Abnormal aggregates of α-synuclein in the form of fibril seem to spread within the central nervous system in a "prion-like" fashion; where fibrillar α-synuclein function as a template for normal endogenous α-synuclein, leading to progressive aggregation and propagation throughout neurons. However, there are still unanswered questions on how and why α-synuclein undergoes initial aggregation in seemingly normal tissues.

The etiology of PD is only partially understood, but it seems to be related to factors promoting initial abnormal aggregates of α-synuclein. Currently, a conceptual model including "triggers", "facilitators" and "aggravators" has been proposed to explain the role of several of these factors in diverse phases of the disease (Johnson et al., 2019). Among "triggers", head trauma, environmental toxins and viral infections are mainly recognized (Johnson et al., 2019). These "triggers" affect tissues that are exposed to external influences, such as the nasal and intestinal epithelium; they are believed to act years or decades before the onset of degeneration of dopaminergic neurons in the SN. The onset of pathology in the gut and olfactory pathways would explain the chronic constipation and the olfactory dysfunction frequently preceding the beginning of motor symptoms in these patients by many years. Considering genetic risk factors, it has been estimated that they represent between 26% and 36% of the risk for PD; moreover, genome-wide association studies have identified 78 genetic loci associated with PD, many of them located close to genes involved in immunological functions and the lysosomal-autophagy pathway (Tilusiak et al., 2019). For example, enrichment analysis combining genome-wide association studies and expression Quantitative Trait Loci data has shown an association with the 6p21 loci containing multiple HLA-MHC-II genes. Patients with PD seem to have specific immune annotations variants in primary T lymphocytes from the blood, rather than in specific brain cells as observed in patients with schizophrenia. This information suggests that a large proportion of the variance explaining the etiology of PD is related to a complex interaction between environmental and genetic factors.

Epidemiological and experimental evidence linking viruses with PD: Some viral infections are known to produce post-encephalitic parkinsonism as part of direct involvement of the CNS; however, the question is whether viruses can contribute to the pathogenesis of PD. Case-control studies and epidemiological surveillances have identified a relationship between some previous viral infections and enhanced risk of PD; these associations would include influenza virus, herpes simplex virus, hepatitis B virus and hepatitis C virus (HCV) among others; however, only infection with HCV has shown a consistent association with PD in meta-analyses (Wang et al., 2020).

Besides this clinical and epidemiological evidence, there are experimental studies showing that viruses may alter the expression and aggregation of α-synuclein in infected cells. In 42 children with a mean age of 12.4 years, suffering gastric and duodenal inflammation or intestinal allograft recipients, studied for levels of α-synuclein in immunostained endoscopic biopsies; gastrointestinal infections with norovirus lead to up-regulation of α-synuclein in the enteric nervous system (Stolzenberg et al., 2017); such increased expression of α-synuclein would lead to increased aggregation, even if the protein is not intrinsically abnormal. Enhanced phosphorylation of α-synuclein promoting its aggregation has been observed in C57BL/6J mouse infected with influenza virus A/Vietnam/1203/04 H5N1, along with loss of dopaminergic neurons in the SN (Jang et al., 2009). The virus is capable to travel from the peripheral to the central nervous system in mice and activate microglia (Jang et al., 2009). A similar finding was observed in CD-1 mice infected with Western Equine Encephalitis Virus with the extent of viral replication controlled using passive immunotherapy, where increased amounts of phosphorylated α-synuclein in the serine 129 residue were found in the entorhinal cortex, hippocampus and basal midbrain (Bantle et al., 2019). More recently, it has been shown that replication of influenza virus (H1N1) can cause severe disturbances in proteostasis (the fine-tuned balance of cellular protein levels) inducing seeds of aggregated α-synuclein in Lund human mesencephalic dopaminergic cells in vitro, but not of TDP-43 or tau protein suggesting a selective effect for α-synuclein (Marreiros et al., 2020). Reinforcing the hypothesis that viral infections can trigger the early pathological findings of PD; however, these studies need confirmation under similar experimental conditions. Moreover, in the majority of these studies, inflammation and abnormal neuro-pathological findings persisted after resolution of the infection, suggesting a "hit and run" mechanism of damage by the studied viruses; this feature would limit the discovery of a similar mechanism in humans.

Viruses can also induce robust inflammatory responses, which can contribute to the pathogenesis of PD by a "hit and run" mechanism of damage to the CNS, occurring when the virus has been cleared and it is no longer possible to find the viral genome or antigens in the affected tissue. Experimental infections to rodents with influenza H1N1 virus, Japanese Encephalitis Virus and Western Equine Encephalitis Virus produced marked gliosis with microglial activation in the hippocampus and SN leading to the pathological and motor findings of PD (Bantle et al., 2019). Moreover, the systemic inflammatory response elicited by some virus such as HCV is believed to increase the risk of PD by damaging dopaminergic neurons; in the latter case, epidemiological studies and meta-analyses have shown a decreased incidence of PD in individuals receiving interferon-based antiviral treatment regimens against HCV at 5-year follow-up (Lin et al., 2019); however, it is not entirely clear whether this observed risk reduction is related to a reduced inflammatory response or a direct antiviral effect on potentially neurotropic HCV or both mechanisms.

Interestingly, α-synuclein has shown to inhibit viral infections limiting the injury to the CNS. There is evidence that α-synuclein has properties similar to the antimicrobial peptides as it has antibacterial activity against *E. coli*, *S. aureus* and some fungal pathogens in the brain. Experimental infections with West Nile virus in α-synuclein-knockout mice have shown to produce a robust increase in viral particles with enhanced neuronal injury leading to shortened survival compared with wild-type or heterozygote mice (Beatman et al., 2015). Moreover, an increase in the amount of monomeric and oligomeric α-synuclein has shown a consistent chemoattractant effect on neutrophils and

monocytes following infection with norovirus (Stolzenberg et al., 2017), suggesting that such inflammatory response is common after exposure to this type of infection. Whether the enhanced expression and inflammatory response induced by the neuro-protective effects of α-synuclein may contribute to its own aggregation is a contentious possibility that requires further investigation.

In summary, epidemiological, clinical and experimental evidence suggests a link between viral infections and the risk of PD. This could be caused by a direct effect in α-synuclein expression and phosphorylation, through an inflammatory response elicited by the infection or a complex interplay between both. Another potentially related mechanism would implicate an impaired degradation of intracellular proteins induced by the virus. This mechanism has been proposed as relevant in the pathogenesis of PD, which leads to an overload and accumulation of misfolded α-synuclein.

Can viruses impairing cellular degradation mechanisms have a role in the pathogenesis of PD? Coronaviruses (CoVs) such as Middle East Respiratory Syndrome, mouse hepatitis virus, and SARS-CoV (a virus causing an outbreak in China in year 2002) seem to alter proteostasis by diverting the cellular quality control pathways that degrade misfolded proteins in order to replicate its viral genome, making cells vulnerable to decreased clearance of aggregated proteins; this is achieved by hijacking the autophagy machinery by generating viral double membrane vesicles (DMVs) in the infected cytoplasm that are unable to fuse with lysosomes, the cellular organelle that ultimately destroys proteins (Reggiori et al., 2010). Besides CoVs, coxsackievirus B3, poliovirus and HCV can also induce DMVs in infected cells, facilitating viral replication and assembly. It is unclear whether this pathogenic mechanism can also account for the increased risk of PD conferred by HCV infections.

Lipidation of the cytosolic microtubule associated light chain 3 I (LC3-I) protein generating LC3-II is considered a key event in the induction of autophagy. This protein is essential for the formation of structures similar to DMVs called autophagosomes. It has been proposed that certain viruses such as SARS-CoV and HCV may recruit non-lipidated LC3 in DMVs. Interestingly, a number of genes causing monogenic inherited forms of PD express proteins implicated in control of autophagy and endomembrane trafficking; among these proteins, LRRK2 has a special relevance as it is the most common hereditary cause of monogenic inherited PD. Evidence suggests that some LRRK2 mutations may decrease lipidation of LC3-I resulting in accumulation of autophagic vacuoles (Roosen and Cookson, 2016). It can be hypothesized that individuals with LRRK2 mutations may be vulnerable to the effects of viruses that sequestrate LC3-I, such as CoVs or HCV, as this would cause an additive effect with even lower levels of LC3-II, further reducing elimination of cellular debris. If the cell survives to the infection, the damaged cellular mechanism for protein degradation may turn the cell even more vulnerable for accumulation of misfolded proteins such as α-synuclein.

In recent months, infection with "Severe Acute Respiratory Syndrome Coronavirus-2" (SARS-CoV-2) has scaled into a pandemic level threatening health-care systems around the world owing to its capacity to cause respiratory failure. SARS-CoV-2 can also cause diarrhea and neurological symptoms including hyposmia, suggesting that the virus has tropism for the gastrointestinal tract and the nervous system. The neurotropic effects of SARS-CoV-2 may be mediated by its S-protein binding to the angiotensin-converting enzyme type-2 receptor, which is highly expressed in neurons. Although the full biology of SARS-CoV-2 is still to be elucidated, the molecular reminiscent between this virus and other CoVs suggests that they may cause similar derangements in cell structures and protein processing.

Conclusions: The role of viruses in the pathogenesis of PD is still controversial. The clinical and epidemiological evidence supports a pathogenic role for HCV; this virus shares similar features to CoVs as both can elicit a strong immunological response, have neurotropic potential and use the DMVs system for replication, potentially impairing the cellular autophagy system. Although common viruses affecting humans such as norovirus and influenza virus have been shown to increase the expression and aggregation of α-synuclein, this evidence remains in an experimental level and it is unclear if they can increase the risk of PD. Whether individuals with underlying monogenic inherited mutations causing PD may have a higher risk to develop PD when they encounter viral "triggers" is a hypothesis that would require further assessments, as PD seems to result from a complex interplay between environmental and genetic mechanisms.

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