The Odyssey of Alpha-synuclein and Neuroinflammatory Mediators as Potential Candidates in the Aetiology of Parkinson's Disease

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Abstract

There is a myriad of potential candidates suggested to be associated to the aetiology of Parkinson's disease, of these α-synuclein appears to the first runner up. This notion is endorsed by the appearance of α-synuclein aggregates (present in Lewy bodies) in close proximity to regions exhibiting neuronal cell loss. The mechanism(s) contributing to its accumulation include, some genetic dysfunction, overproduction of the protein, misfolding, inability to effectively degrade the misfolded form. Furthermore, the ability of α-synuclein to operate as ferrireductase, allows it to produce reactive oxygen species and exacerbate the oxidative stress related cytotoxic processes in the illness. The accumulation of misfolded α-synuclein may also invoke the release of inflammatory mediators. The presence of microgliosis in the substantia nigra in the disease reflects the occurrence of inflammation. The destructive role of neuro-inflammation in degenerative diseases is exhibited by the neurological manifestations produced by infectious agents such as bacteria and viruses. Therefore, these findings offer many budding therapeutic interventions that can be advocated in the disorder. However, an urgent need for a biomarker is warranted to detect the disease early in order to halt or delay its progression.

The neurodegenerative disorder Parkinson's disease (PD) is hallmarked by the presence of cytoplasmic inclusions, Lewy body (LB) and ravaged dopaminergic neurons in the substantia nigra pars compacta (SNc). LB are primarily composed of aggregates of the protein α-synuclein. Although the precise aetiology underlying the illness remains obscure, a medley of factors has been postulated. There are a multitude of factors that have been implicated including, ageing, genetic predisposition, endogenous/exogenous toxins, iron, oxidative stress, mitochondrial dysfunction, misfolding of proteins (such as α-synuclein), inefficient clearance of rogue proteins, infectious agents (such as viruses) and neuroinflammation. This list is not exhaustive and current findings suggest other evolving influences. More importantly, it is highly likely that rather than operating independently, these formidable culprits intermesh to invoke cytotoxic processes resulting in severe neuronal causalities in its wake. This concords with the notion of a multifactorial aetiology for PD [1].

In the event of a neurodegenerative illness or infection, microglia is activated. This idea is supported by the presence of HLA-DR- positive or class II major histocompatibility (MHC class II antigen) reactive microgliosis in SN in PD [2]. Similar findings were reported from *in vivo* PET imaging in PD patients [3]. These results may be significant to the pathogenesis, since microglia constitute to the major antigen-presenting cell during neurodegeneration. This phenomenon is demonstrated by the presence and propagation of activated microglia in other diseases such as Alzheimer's disease, amyotrophic lateral sclerosis and prion disease [4]. So, it appears to be a part of a common and shared pathway leading to neurodegeneration. This is indicative of the occurrence of neuro-inflammatory
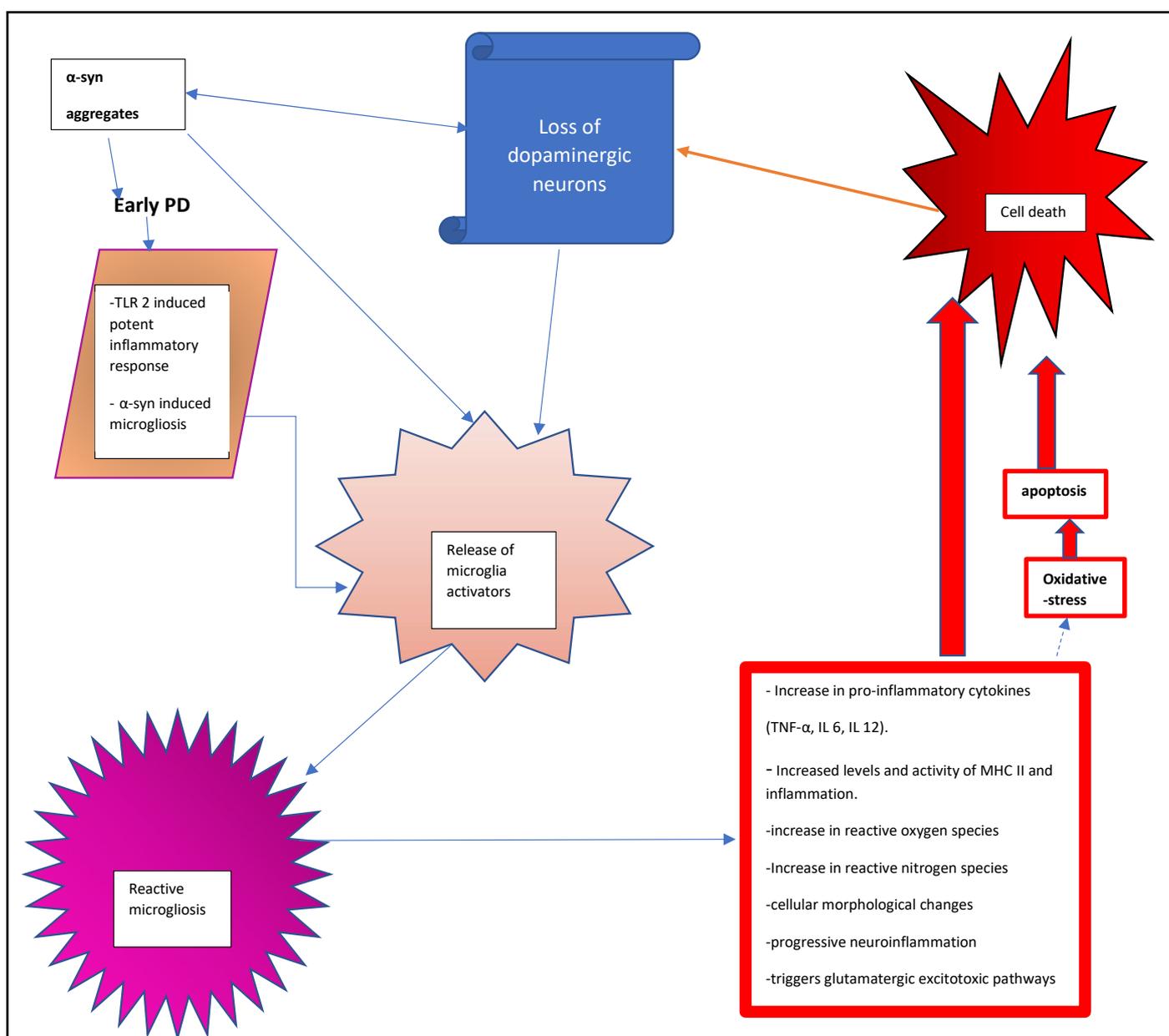
Figure 1: Microglia activation, chronic inflammation in the substantia nigra of Parkinson's disease. Misfolded alpha-synuclein aggregates may contribute to the elevation of Toll-like receptor 2 (TLR2) in the early/ asymptomatic phase of Parkinson's disease, thus suggesting an association between two. Consequently, the TLR2 may evoke a potential neuro-inflammatory response via microgliosis and cytokine inflammatory reactions. The reactive microgliosis can induce an array of cellular catastrophic toxic processes including pro-inflammatory cytokines production, an elevation of class II major histocompatibility (MHC II), reactive oxygen species induced oxidative stress. Subsequently, these processes may provoke cellular dysfunction and eventual destruction. The neuronal death itself may in turn stimulate microgliosis via microglia activator and thus setting off the inflammatory cycle again. Thereby precipitating a chronic state of neuro-inflammation. TNF-α: Tumour Necrosis Factor Alpha ; IL 6: Interleukin 6; IL 12 : Interleukin 12.

processes, since under physiological conditions the microglia cells express low levels of MHC II molecules, thereby suggestive of an ongoing degenerative process during the illness (Figure 1). It supports the notion that the immune responses may execute an integral role in the development and/or progression of the pathophysiology. This notion is supported by the reduction of risk or delay in progression of PD by the administration of the nonsteroidal anti-inflammatory drug, ibuprofen [5,6]. More importantly, transcriptomic studies in these diseases

illustrated an upregulation of genes for HLA-DR [7], which suggests that the inflammation feature observed in these diseases is derived from HLA-DR genetic predilection.

At present it is unclear whether microgliosis is a component of the primary artillery or a manifestation of the degenerative processes, nevertheless it very likely contributes to the resulting cellular carnage. Microglia can operate as either neuroprotective or destructive agents [8]. Thus, it is possible that it exerts both a malevolent and protective role. Indeed, microglia activated by lipopolysaccharide or TNF-α, are denoted as the "M1" type, that is pro-inflammatory and plays a central role in the defence against pathogens and tumour cells via the production of cytokines (including, TNF-α, IL-6 or IL-12) and reactive free radicals. In contrast, the "M2" type is neuroprotective by virtue of its actions such as release of anti-inflammatory cytokines (such as, IL-4, IL-13 or TGF-β) and stimulates angiogenesis [9].

Perhaps the initial consequence of microgliosis is neuroprotective, since it augments phagocytosis and the clearance of misfolded proteins such as α-synuclein. Thus, they endeavour to maintain neuro-immunological homeostasis to protect the cells. It is also relatively selective, since activation of microglia and consequent reactive processes may be customised to different trigger pathological events or rogue molecules . For instance, zinc released from neurons (probably synaptic vesicles), in animal models of cerebral ischaemia provokes microglia activation [10].

However, subsequently a chronic state of inflammation (Figure 1) may result in the release of cytokines from the activated microglia , which may elicit cytotoxic pro-inflammatory pathway(s). Indeed, *in vitro* studies suggest that pro-inflammatory cytokines can induce MHC class II antigens present on microglia. These findings concord with the elevation of cytokines, potent regulators of cell growth and apoptosis-signalling receptor molecule, TNF alpha, IL-1β, IL-12,IL-6, sFAS, EGF, TGF-alpha, TGF-β1, bFGF, β2-MG) found in the striatum in PD [11-16]. Thus, cytokine release may represent a potential target site for drug treatment in PD and they may delay the degenerative processes and thus the progression. Additionally, a dual role for microgliosis has also been hypothesized in Alzheimer' disease [17].

Exposure to the neurotoxin 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) produces irreversible dopamine neuronal destruction and parkinsonian syndrome in man and primates. Interestingly, subjects in contact with MPTP showed microgliosis to be maintained for around 16 years after exposure. This is suggestive of a chronic state of neuroinflammation and also highlights its relevance to the idiopathic form of PD [18]. Furthermore,

animal studies using neurotoxin such as MPTP and 6-hydroxydopamine [19], suggest that microglia activation is stimulated by the initial destruction of dopamine cells, thereby representing a secondary effect. However, lipopolysaccharide stimulated microglia (probably of the M1 type) have also shown to exert cytotoxic actions on the dopaminergic neurons in both *in vivo* and *in vitro* studies [20]. Also, the T cells may conspire with the active microglia to execute neuro-destruction. In turn, the cell destruction may result in stimulation of additional immune reactions and cascade greater destruction of the neuron population, thereby endorsing the ambivalent role of the activated microglia and the close association of inflammatory organisation to neuronal death.

Neuro-inflammation appears to be a promising contender in the fabric of degenerative processes in PD particularly since the nigral dopaminergic neurons are particularly susceptible to the cytotoxic processes related to oxidative stress and neuro-inflammation. This is supported by the presence of inflammation in the SN in PD, where there is marked cell loss. Interestingly, toll-like receptor 2 (TLR2) is markedly expressed in reactive microglia in the asymptomatic phase of PD, incidental Lewy body disease (Figure 1). TLR2 facilitates α-synuclein mediated activation of microglia. However, this phenomenon is not observed in PD, thereby reflecting an early pathological reaction(s) when the dopaminergic neuronal loss is less marked since, incidental Lewy body disease exhibits around 40% nigral cell loss in contrast to 82% loss in the symptomatic PD [21]. This suggests, firstly that microgliosis is not only provoked by dopaminergic neuronal death but also by TLR2 linked α-synuclein and secondly an involvement of inflammatory processes in the initial stages of the disorder. Additionally, perhaps some genetic defects may ascribe for the malevolent role adopted by the microglia. Indeed, mutations in microglia have contribute to marked behavioural syndromes in mice.

Subsequently, as the disease progresses and there is more marked neuronal loss this may augment the cytotoxic contribution from the inflammatory system. There may be a genetic component related to the faulty or dysfunctional immunological dynamics, so exposure to infectious mediators may initiate a cascade of cytotoxic events, which may be linked to the misfolding and aggregation of α-synuclein [22]. Alternatively, α-synuclein may be frontline candidate in the neuronal destructive force [23].

The physiological role of α-synuclein includes participation in the release of neurotransmitters and more importantly in synaptic plasticity [24]. It appears to exist in unfolded monomeric (or tetrameric) form. However, under pathological conditions it alters from soluble to insoluble fibrillary structures chiefly contributing to misfolding of the protein. Subsequently, accumulation of α-synuclein

appears to give rise to pathological LB structures. The presence of these neuronal inclusions in the SN is vital for diagnosis of PD at post-mortem [25], although they are also found in other neurodegenerative disorders. In view of the occurrence of LB in close vicinity to areas exhibiting marked neuronal loss, coupled with its presence in early asymptomatic PD or incidental Lewy body disease [25], lends support to the concept that α-synuclein may be lead character in the pathogenesis of PD [26]. Indeed, in accordance to Braak [27] proposed scheme for staging PD, two vital points are highlighted , firstly that α-synuclein pathology is present in the initial stages (stage 1 in the vagus nerve and olfactory nucleus) and secondly during stage 3 α-synuclein appears in the substantia nigra and this is associated with the manifestation of early motor deficits. There is an absence of α-synuclein pathology when there is only a marginal 12% nigral cell loss, whereas the appearance of α-synuclein aggregates in the neuromelanin containing SN demonstrated a significant correlation to dopaminergic neuronal death. Perhaps the amasses of α-synuclein prompts cellular cytotoxic chaos in these vulnerable dopaminergic nigral neuronal functioning resulting in their destruction. In addition, mutations of α-synuclein gene has been linked to the familial PD [28].

A genetic variability in α-synuclein has been implicated in idiopathic PD. Indeed, its accumulation has been attributed to the α-synuclein locus triplication [29]. This genetically driven aggregation of α-synuclein may activate microglia in an attempt to degrade the α-synuclein accumulation and precipitate neuro-inflammation (Figure 2). Indeed, microglial astrocytes and neurons have the potential to breakdown the accumulated α-synuclein by internal degradative mechanisms [30]. Under physiological conditions, macrophages break down α-synuclein via lysosomal and proteolytic pathways, however perhaps in the pathological state these degradative mechanisms are compromised or overwhelmed by the excess manifestation of these oligomers. It seems plausible that α-synuclein aggregates initiate neuro-inflammatory mechanisms (adaptive immunity).

Over expression of the native form of α-synuclein lends a predilection to its misfolding (Figure 2), accumulation and subsequent formation LB [31]. This may be attributed for the tendency for the native or wild type α-synuclein to nitrate modification which augments its susceptibility to aggregate [32]. The nitro-tyrosine modified α-synuclein elicits T lymphocytes proliferation and neuronal destruction. Indeed, specific peptides on α-synuclein are recognised by T cells which provoke its cellular destructive reactions [33]. The nitrated form of α-synuclein was detected in MPTP treated mice, and interestingly this form of the protein generated T cells coupled with neuro-inflammation and exacerbated destruction of dopamine cells. Similarly, an infiltration of $CD4^+$ and $CD8^+$T cells

(Figure 2) was found in the PD brain [34]. The cytotoxic T cell actions observed in the dopaminergic neurons in PD was chiefly orchestrated by $CD4^+$ T cell associated with Fas ligand. This notion is supported by the build-up of $CD4^+$ T cells in protracted neurodegeneration. It therefore appears that α-synuclein not only stimulates neuro-inflammation via T cells of the adaptive immune system, but also maintains it [35]. In addition, since the B cells are often reported to be reduced in illness, humoral immunity may also been involved in pathogenesis of PD. Alternatively, there is a possibility of that an earlier affiliation or encounter with an infectious agent such as a bacteria or virus, which may somehow impact the immune system conferring to the susceptibility to induce neurodegeneration.

In the early stages of the illness peripheral inflammation appears to be entangled in the initiation and manifestation of non-motor symptoms (Braak stages 1-2). The bacteria *Helicobacter pylori* induced gut infections have been related to the progression of PD. This idea is supported by the motor improvement observed in PD patients after treatment for *Helicobacter pylori* [36]. It therefore appears chronic gut related infections may signal inflammation (via pro-inflammatory mediators) via the gut-brain axis to the brain and fund the progression of degeneration by deploying inflammatory troops such as cytotoxic cytokines.

Indeed, the overexpression of the gram-negative bacteria *Proteus mirabilis* in PD mouse model, exhibited destruction of dopamine neurons and inflammation in the SN coupled to the presence of α-synuclein aggregates in the brain and gastro-intestinal tract [37].

Many patients afflicted with encephalitis lethargica (1915-1927), exhibited parkinsonian extrapyramidal like features during the chronic phase of the infection that occurred months or years later [38-42]. However, viral antibodies, RNA, viral particles or inclusions could not be detected in many studies [43-48]. These data are in contrast to those reported by others [49-51]. This idea is supported by the association of influenza (and other viral infections) to post-encephalitic parkinsonism. A positive correlation was demonstrated between severity of influenza and the occurrence of PD in a population-based study [52]. Interestingly in viral infections cytotoxic $CD4^+$ T cells have been reported to exert a key part in the observed immune reactions. In a study they found that exposure to dioxin compromised the cytotoxic T cell response against the influenza A virus in mice [53]. Collectively, these findings are indicative of the operation of a toxin or "an infectious agent", which causes the immune system to turn hostile against the nigral neurons. However, α -synuclein containing Lewy bodies have not been demonstrated in post mortem brain tissue of postencephalitic parkinsonism [54]. This opens the possibility of many

potential candidates in the pathogenesis of PD including environmental toxins such as dioxin, pesticides, virus, bacteria, etc. The presence of these entities coupled with neuronal cell vulnerability related to aging and genetic predisposition probably prompts the abnormal regulation of inflammatory reactions, this may in turn exacerbate neuronal destruction observed in PD.

Experimental long-term studies with H5N1 influenza virus show that H5N1 induces transient loss of dopamine in the SNpc and basal ganglia. In addition, activated microglia and increase in cytokines could be detected suggesting, that viral infection is not excluded as trigger for Parkinson's disease [17]. Acute onset of West Nile virus infections induces parkinsonian like symptoms associated to the loss of dopaminergic neurons in the SN and an elevation of α-synuclein. The α-synuclein appears to exert a cellular protective role since it inhibits RNA viral infection associated injury [55]. Unfortunately, there are only few reports on viral brain infection in contrast to those on the degenerating potential of HIV. Recent work related to molecular pathology of Neuro-AIDS/CNS-HIV, has clearly shown neuritic α-synuclein in the SN of 16% HIV cases and β-amyloid deposits in most of the HIV positive cases [56,57]. Mackiewicz and colleagues [57] suggested that there may be a common pathogenic mechanisms between HIV and aging, which may promote pathways involved in Alzheimer's disease or Alzheimer related dementias including triggering β-amyloid, Tau- or α-synuclein pathology.

Post-mortem findings have demonstrated a significant decrease of the numerical density of total neurons, as well as of pigmented neurons in the SN of patients with HIV-1 infection [58]. For modelling HIV-1 long term symptomology, rhesus monkeys infected with the simian immunodeficiency virus (SIV mac 251) were employed and these studies showed the dopaminergic system to be markedly affected with an increase in dopamine turnover [59]. Using HIV-infected T-lymphoblasts ACH-2 to elucidate the effects of HIV on dopamine, a dopamine induced concentration-dependent HIV activation was reported [60]. Glutamatergic pathology (Figure 1) is of major interest in HIV induced dementia [61]. It has been suggested that the NMDA-receptor channel antagonists' amantadine and memantine may be a suitable therapeutic option for both parkinsonism and dementia observed in late phases of HIV infection [62].

In addition, primary macrophages, neuroblastoma and glioblastoma cell lines exposed to HIV-1 indicated the operation of oxidative stress as the mechanism of degenerative processes involved in HIV-1 infection [59]. However, others have suggested that impaired repair mechanisms due to a deficiency of S-adenosylmethionine facilitates cytokine and/or oxygen mediated toxicity

underlying vascular myelinopathy and neuronal damage in AIDS [63]. Furthermore, it has been shown that the DAT 10/10-repeat allele T3 is more frequent in HIV individuals. Subjects homozygous for the 10-repeat allele had higher amounts of CSF dopamine and reduced DATmRNA expression but similar disease severity compared to those carrying other DAT genotypes [64].

Recently, Helms and co-workers found encephalopathic features in patients with severe covid-19 or SARS -Cov -2 [65]. The neurological features included, confusion, cognitive difficulties, poorly organised movement in response to command. Although it is too early at present to predict and also the situation is evolving, nevertheless, this sinister virus appears to have the potential to manifest some permanent long-term neurological defects.

Intriguingly, α-synuclein has also been suggested to operate as a natural antimicrobial peptide (AMP) at the front line of defence against invading pathogens (a component of the innate immune system). So, perhaps in the event of an attack by a pathogen, the α-synuclein comes to the defence initially, however it may undergo pathophysiological changes in the disease process (and in patients where it is overexpressed) resulting in its oligomerization, misfolding and subsequent accumulation.

The oligomerised form of α-synuclein can elicit neuronal destruction via membrane disruption, disruption of function of vital cellular organelles such as mitochondria and impairment of protein degradation. Thus, the aggregates of rogue α-synuclein (that is LB) may be responsible for the reduction in activity of mitochondrial complex I reported in SN in PD. These oligomerised α-synuclein may compromise the protein degradative mechanisms, thereby resulting in their accumulation. The ubiquitin-proteasome system and chaperone-mediated autophagy that are responsible for protein degradation may be overwhelmed by the build-up of the misfolded α-synuclein (Figure 2). It is also possible that they may not be fully operational under pathological conditions [23]. Subsequently, α-synuclein pathology propagates to neighbouring cells in a "prion-like" fashion.

There are an array of factors which may contribute to the misfolding of α-synuclein, including familial PD related missense point mutation of α-synuclein gene, and some of them may affect the micro-environment for instance: a decrease in pH, an increase in temperature, amphipathic molecules (such as herbicides/pesticides), molecular crowding, polyamines, proteoglycans, chaotropic agents and metal ions [66]. Metal ions neutralise charge repulsion, which favours α-synuclein to a more condensed and aggregate-prone structure. It appears that the ability for metal ions to boost α-synuclein fibril formation is related to the ion charge density. Di- and trivalent metal
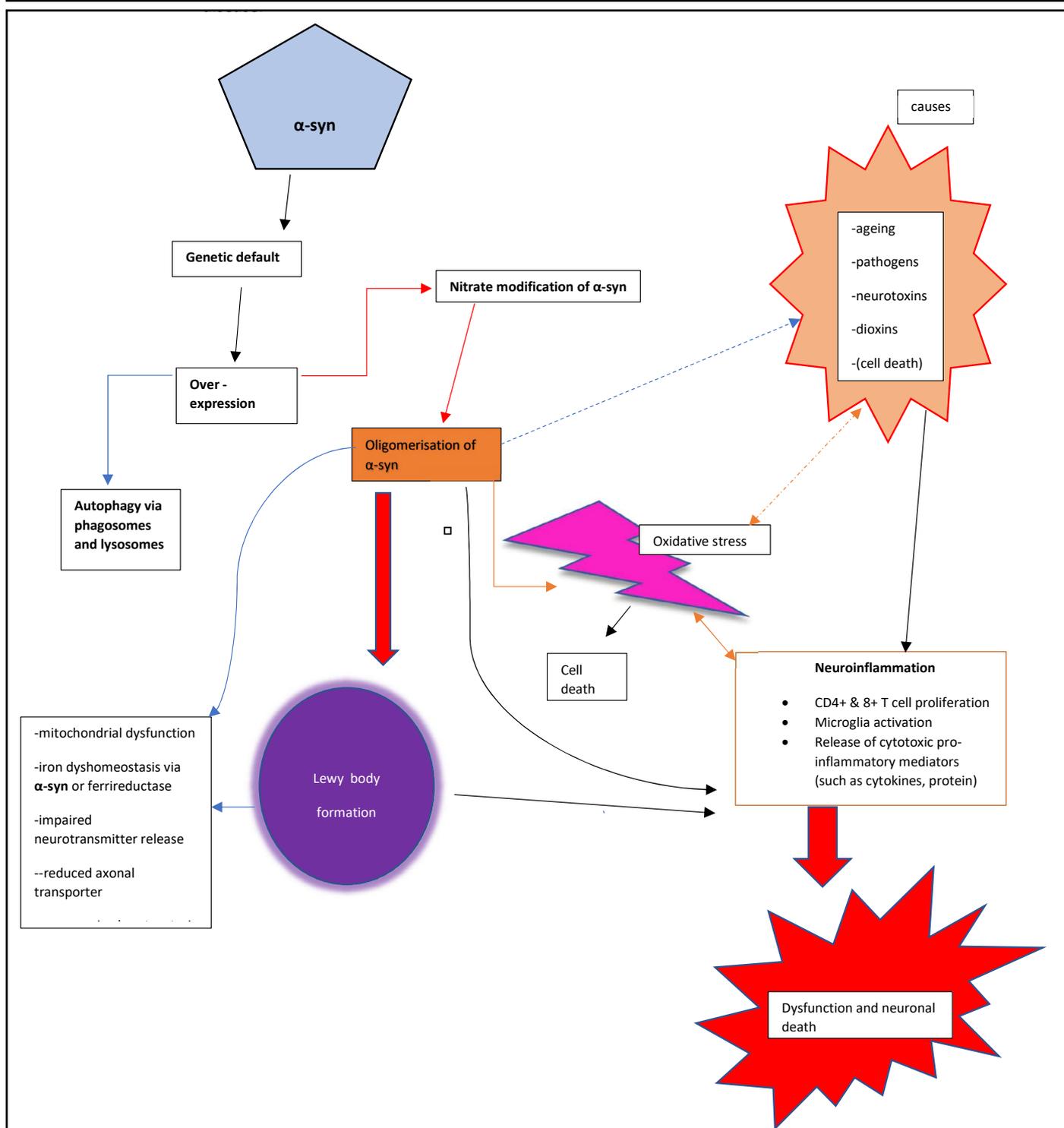
Figure 2: Alpha-synuclein (α-syn) and neuro-inflammatory related cytotoxic pathways in Parkinson's disease. An overview of potential causes and an association between alpha-synuclein and neuro-inflammatory processes resulting in pathological pathways leading to the characteristic nigral neurodegeneration in Parkinson's disease. A genetic dysfunction may contribute to the over expression of alpha synuclein. This may overwhelm the autophagy protein clearance system, resulting in its accumulation. Subsequently, the elevated alpha synuclein may undergo nitrate modification, which favours its oligomerisation and aggregation. These alpha-synuclein aggregates lead to the formation of Lewy bodies and can trigger neurodegeneration via processes such as oxidative stress, neuroinflammation, mitochondrial dysfunction, iron dyshomeostasis.

ions such as aluminium, Iron (III), Copper (II) have been reported to be markedly efficient in this aspect [23].

Fascinatingly α-synuclein is able to operate as cellular ferrireductase. This enzyme reduces iron (III) to iron (II) using copper as a co-factor. In PD, a marked elevation in iron (III) and total iron has been reported in the SN [67]. Perhaps the α-synuclein/ferrireductase (Figure 2), is malfunctioning due to pathology of the disease or some genetic abnormality or endogenous/exo-toxin, this may result in disturbing the physiological iron homeostasis resulting in the deposition of iron [26]. The raised iron (III) content in SN may further exacerbate the neuronal destruction via augmenting of α-synuclein misfolding and accumulation, neuronal death via triggering cytotoxic processes such as oxidative stress.

Conclusion

There is compelling evidence supporting the involvement of the misfolded α-synuclein aggregates in the aetiology and pathogenesis of PD. There are number of mechanisms related to α-synuclein related neurotoxicity including toxic gain/loss of function, mechanical destruction of cellular processes/compartments. It is also possible that there are more than one-type of α-synuclein toxic aggregate, which may in turn employ different routes to induce neuronal death. These findings clearly demonstrate the malevolent actions of α-synuclein. It is therefore key to elucidate factors and mechanism(s) underlying the misfolding and accumulation of α-synuclein as this would provide an insight to the pathogenesis of the disease and thus effective treatment to halt its progression. However, it is unlikely that only a dysfunctional and threatening α-synuclein operates independently, it is rather more likely that other features such as genetic components, environmental factors, inflammatory agents are likely to make up this grand neurodegeneration orchestra. Neuro-inflammation observed in the nigral neurons may represent an epiphenomenon to the destruction of the dopaminergic cell loss in the SN in the early stages of the disease. However, it may subsequently contribute the nigral neuron fatalities.

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