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Parkinson's Disease and the Immune System

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1. Introduction

The characteristic neuropathological markers of PD are the presence of Lewy bodies, containing modified α -synuclein amongst other proteins, in the surviving neurons, and the degeneration of neuromelanin-containing dopaminergic neurons in the substantia nigra pars compacta region of the brain. In addition, the progressive nature of PD is characterised by chronic innate inflammation with microglial activation, as well as astrogliosis and lymphocytic infiltration, which are implicated in both the initiation and progression of PD (Qin et al., 2007). Activation of microglial cells will increase the activity of NADPH-oxidase, (with the release of reactive oxygen and nitrogen species). In addition, mitochondrial dysfunction as well as cytotoxicity, (via glutamate release) will occur, which will contribute to the pro-inflammatory state. Abnormal proteasome function in PD contributes to the build up of α -synuclein aggregates within specific brain which will contribute to inflammation through the activation of microglia (reviewed in Crichton and Ward, 2006). Alterations in the innate and adaptive immune systems are reported in PD and will be reviewed in this chapter. Furthermore, considerable evidence over the past few years has indicated that there is a generalised inflammatory response in PD, that is present in both the brain and the periphery. Therapeutic intervention to retard such inflammation may reduce the progression of neurodegeneration in PD.

2. Immune system overview

The immune system is an intricate network of specialised tissues, which protects the host from infection. It can be divided into two interactive systems, innate and adaptive immunity.

2.1 Innate immune system and inflammation

Innate immunity is characterised by the immune system's ability to rapidly mobilize a response to an invading pathogen, toxin, or allergen, by distinguishing self from non-self. Toll like receptors, (TLRs), as well as nucleotide binding and oligomerization domain, (NOD-like receptors) and the cytoplasmic helicase retinoic acid inducible gene protein 1, (RIG-I-like receptors), are located on the phagocytic cell membranes, (e.g. macrophages and microglia) (**Figure 1**). These play a fundamental role in innate recognition of neuronal

damage, by sensing pattern recognition receptors, (PRRs), on endogenous danger-associated molecules e.g. NOD-like receptors, (Reviewed in Ward et al., 2010). Activation of inflammatory gene transcription and post-translational processing will then occur. Innate immunity is present at birth, the effector cells being mostly myeloid cells, neutrophils, monocytes and macrophages, which on activation, release immunoactive substances such as cytokines, neurotrophic factors, chemokines, reactive oxygen and nitrogen species. In addition, a number of inhibitory pathways are induced during this pro-inflammatory stage, which ensure that the elevation in cytokine response does not overwhelm the host.

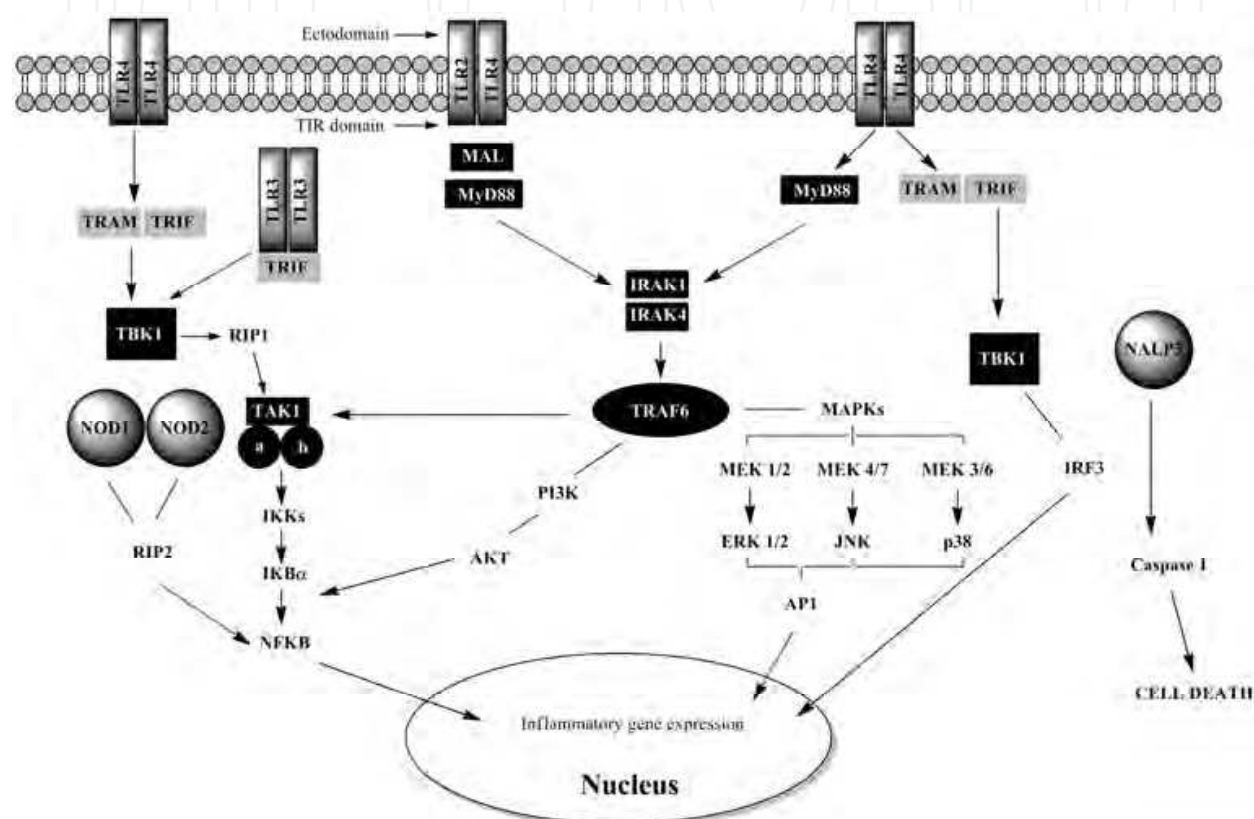


Fig. 1. Danger signals from the external environment or the cytosol are transduced through adapter protein pathways to the nucleus. TLR4 plays a major role in the activation of the immune responses.

Microglia, a subset of glial cells (the other two being oligodendrocytes and astrocytes), are regarded as the resident immuno-competent effector cells of the innate immunity in the brain. (**Figure 2**). In normal circumstances, they have two important roles; a) as surveillance cells, to regulate and supervise the removal of cell debris after neuronal death, after which the microglia will return to their quiescent state, and b) controlling apoptosis. Microglia originate either from circulating monocytes or precursor cells that colonise the nervous system primarily during embryonic and foetal periods of development (reviewed by Chan et al., 2007). Microglia are considered to be primary mediators of neuroinflammation and, as such, have a vast repertoire of PPR as well as TLRs and phagocytic receptors. In the healthy adult brain they exist in a non-activated state, equipped with receptors for neurotransmitters, neuropeptides, hormones and immune signals. Activated microglia show a phenotypical repertoire which include the synthesis of MHC class 1 and II antigen

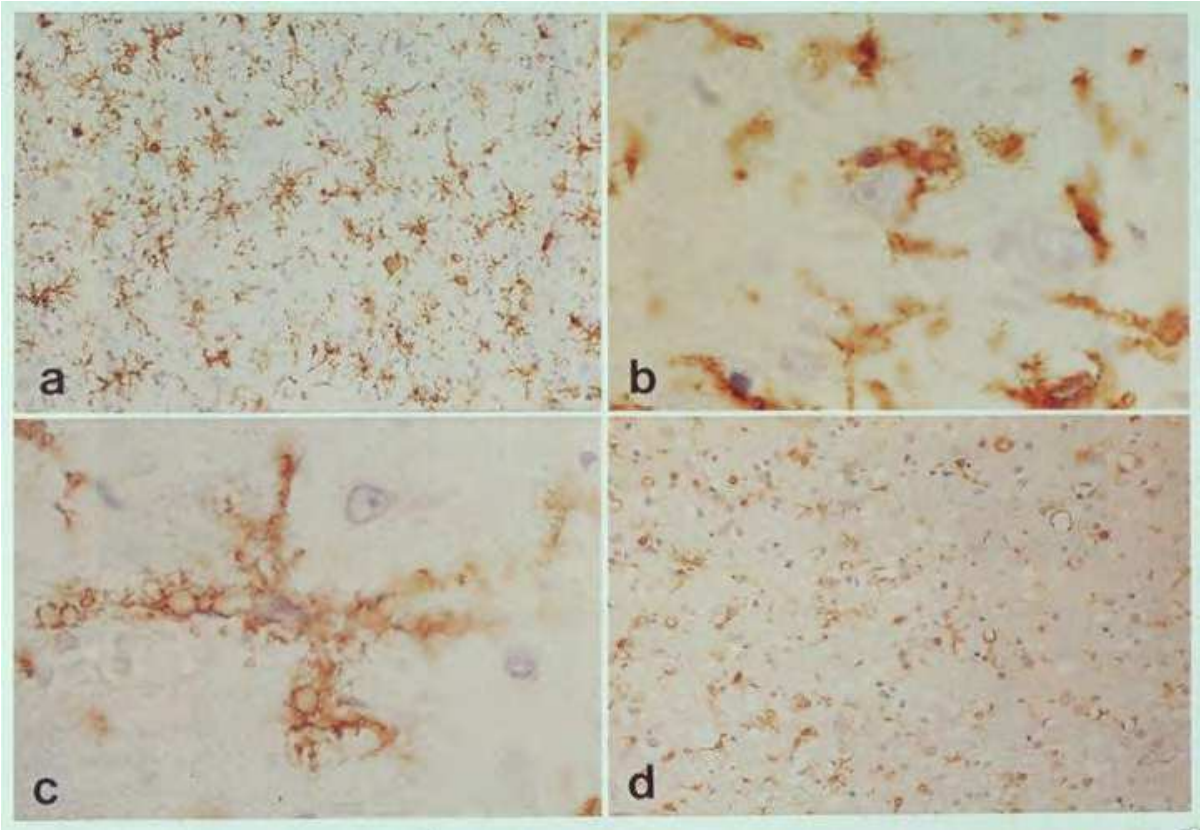


Fig. 2. Activated microglia showing highly branched processes in the ramified state.

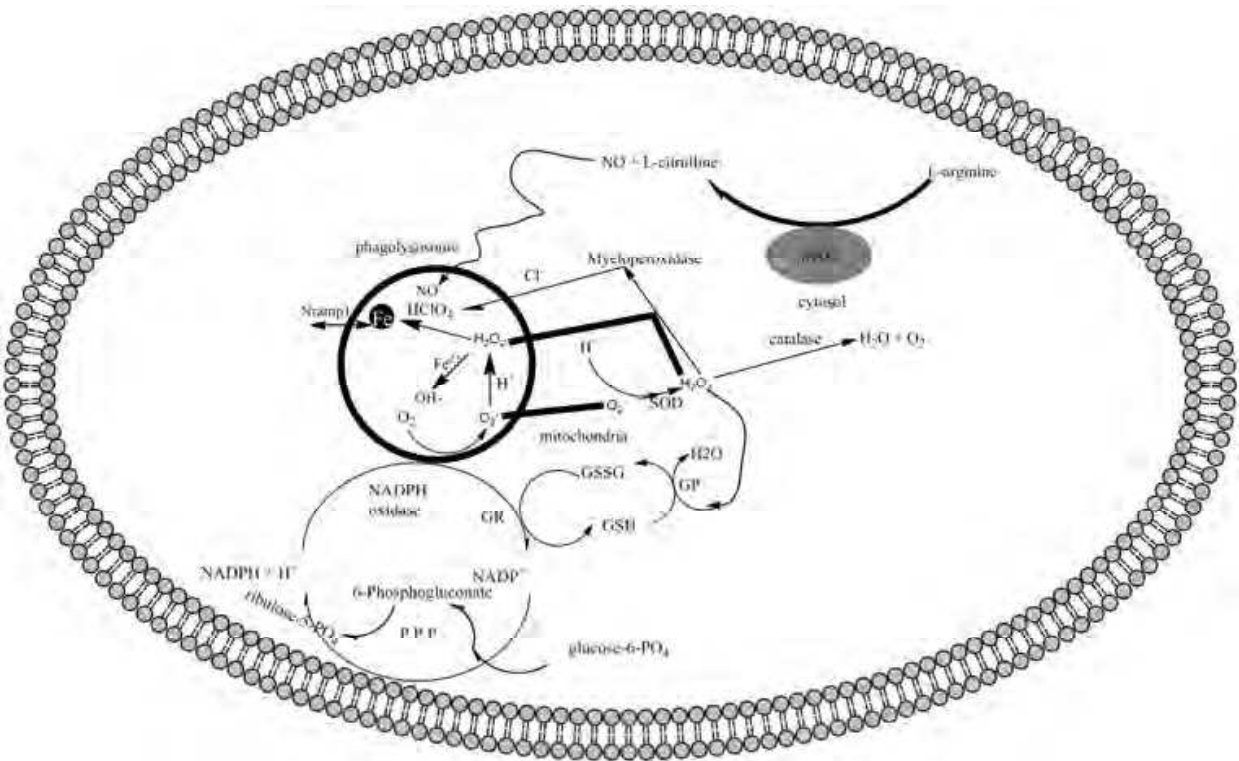


Fig. 3. Activated microglia showing NADPH oxidase activation and the subsequent generation of superoxide and nitric oxide.

presenting proteins, release cytokines such as IL-1, IL-2, IL-6. TGF- α 1, CREB, the synthesis of complement components and their receptors, together with the mitogens M-CSF, GM-CSF and IL-3, **Table 1**. Cytokines are low molecular weight proteins, which modulate microglial activation by binding to their receptors, which are expressed on microglia. Pro-inflammatory cytokines e.g. IL-6, have the ability to elicit a sustained immune response while anti-inflammatory cytokines e.g. IL-10, down-regulate the immune response by binding to appropriate receptors on microglia and initiating an autocrine signalling process. Cytokine effects on the CNS function include growth promotion, inhibition and proliferation of astrocytes and oligodendrocytes, modulation of neurotransmitter release, long term potentiation which is linked to memory formation, and anxiety. Microglia also show a strong respiratory burst capacity, via NADPH oxidase, as well as the ability to release cytotoxic cytokines such as TNF α , and can produce both reactive nitrogen and oxygen species, (**Figure 3**). In normal circumstances, the inflammatory response would be rapid, decisive and then decline. In PD it is hypothesised that microglia priming may alter brain homeostasis. Furthermore, Perry (2004) proposed that chronic exposure to pro-inflammatory signals from systemic infection during an individual's lifetime, might promote an exaggerated microglial response that could contribute to neuronal deterioration, instead of facilitating a protective homeostatic response.

Cytokines	Chemokines	Receptors	Additional factors
IL-1	IP-10	CCR2, 3, 5	MHCI, II
IL-6	MIP1a	IL10R	CD80,86
IL-10	MIP1b	IL12R	CD95, 178
IL-12	MCP1	IL18R	Complements
IL-18	IL-8	IFN R	COX-2
TNF	RANTES	F	
TGF		TGF R	Superoxide
		FCyRI-III	Hydroxyl radical
		CR1 3,4	PGE2
		Prostaglandin receptors	PGD2
			NGF, BDNF

Table 1. Changes in mRNA expression of iron genes involved in iron homeostasis in the substantia nigra and cortex of PD patients compared with controls in post mortem tissue

3. Inflammation in PD brain-innate immune response

In early studies, McGeer et al., (1998) presented evidence for neuro-inflammation in the substantia nigra, (SNc) of PD patients with high numbers of activated microglia particularly in the vicinity of the degenerating neurons. This has been substantiated in many other studies (Dauer and Przedborski 2003; Bartels and Leenders 2007; Gao and Hong 2008). Furthermore increased levels of pro-inflammatory cytokines, e.g. TNF α , IL1 β , IL-2 and IL-6, as well as β 2 microglobulin, epidermal growth factor, transforming growth factor, cyclooxygenase 2 and reactive oxygen and nitrogen species are evident, post mortem, in PD brains (reviewed by Qian et al., 2010), as well as the cerebrospinal fluid (Hald and Lotharius, 2005). More recently, single positron emission tomography (PET) has shown that levels of

[11C] (R)-PK11195, an isoquinoline carboxamide which binds selectively to the peripheral benzodiazepine receptor (PBR), (also known as the mitochondrial 18 kDa translocator protein or TSPO) a selective marker for activated microglia is significantly higher in PD patients than control subjects and correlated with dopaminergic terminal loss, as assayed by [11C] CFT BP (Ouchi et al., 2009). Whether the activation of microglia is an initial event in the development of PD or as a consequence of the degeneration of dopaminergic neurons remains unclear. However it would seem that there is a self perpetuating cycle whereby microglia remain continuously activated and hence represent a suitable drug target. A variety of factors will contribute to this inflammatory process:

Release of ATP from damaged neurons and/or astrocytes will initiate a rapid microglial response towards the site of injury (Davalos et al., 2005), **Figure 4**. In culture it has been shown that extracellular ATP will induce rapid microglia ruffling and whole cell migration, which is mediated via G-protein-coupled P2Y receptors (Honda et al., 2001). Extracellular ATP is also released from CD4⁺ helper T cells, upon stimulation of the T cell receptor. This also plays a crucial role in protracting the TCR-initiated activity of MAPK and secretion of IL-2, thus determining productive T cell activation. Recent published research indicated that ATP also inhibits the generation and function of regulatory T cells via the activation of purinergic P2X receptors (Shenk et al., 2011). Release of ATP from damaged neurons and/or astrocytes will initiate a rapid changes in astrocyte function. Activated astrocytes are present in the regions of the degenerating SNc, which will contribute to the elevated cytokine

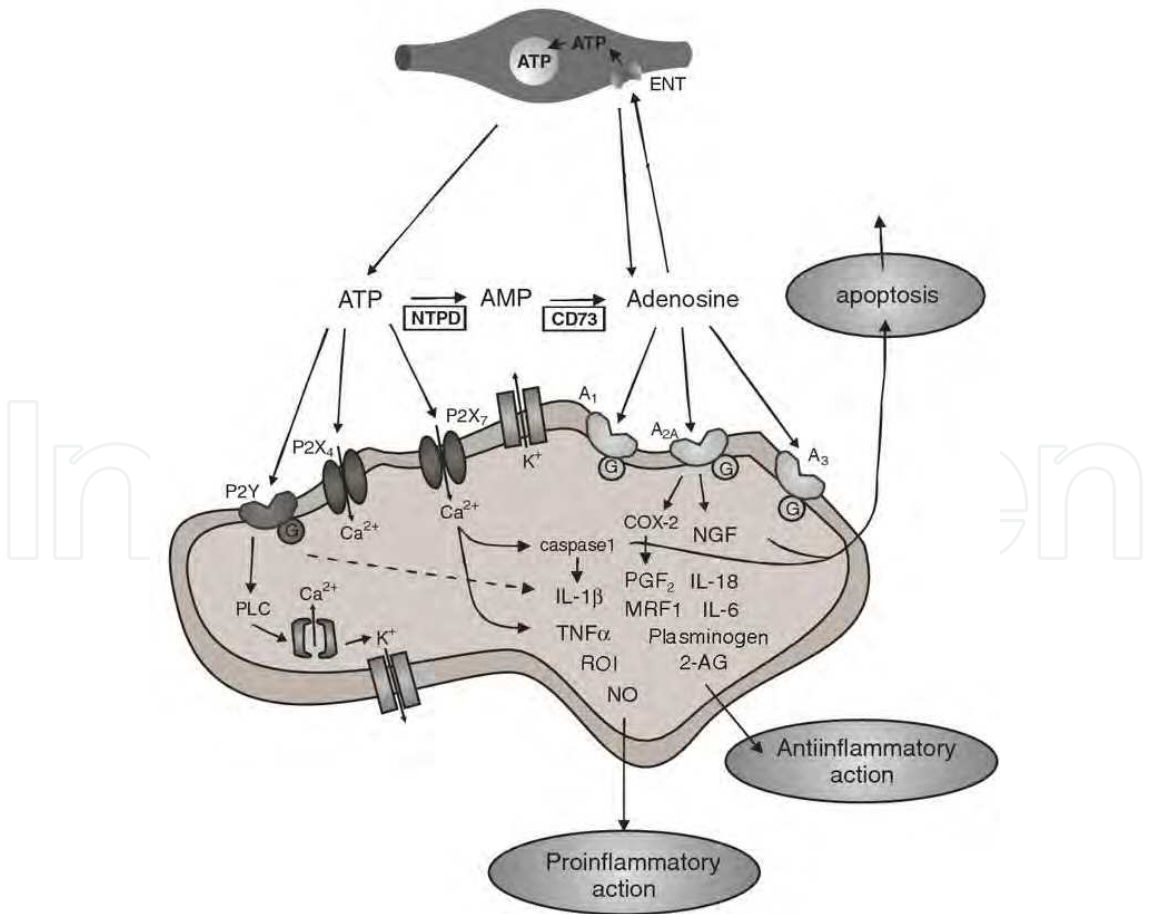


Fig. 4. Release of ATP from damaged neurons (adapted from Davalos et al., 2005).

content in this region (Forno et al., 1992). Some studies have identified a loss of astrocytes in the substantia nigra pars compacta of PD brains by comparison to controls (Damier et al., 1993). Such losses of astrocytes may imply a loss of neurotrophic support for neurons. However this has not been confirmed in other studies of PD brains (Mirza et al., 2000).

Abnormal accumulation and aggregation of α -synuclein occurs in PD. The amyloid fibril of α -synuclein will aggregate to form Lewy bodies, **Figure 5**. Such Lewy bodies will attract activated microglia (McGeer et al., 1988). Iron, which is increased in PD, will enhance intracellular aggregation of α -synuclein which leads to the formation of advanced glycation end products. In addition, there maybe an interaction between α -synuclein and Fe^{2+} to liberate hydroxy radicals, thereby contributing to the oxidative stress (Crichton & Ward, 2006).

Matrix metalloproteins, (MMPs) are proteolytic enzymes which activate microglia. Neuronal cells, in particular in dopaminergic neurons, release MMP-3 which is increased in response to various forms of cellular stress (Kim and Hwang, 2011). Thus will activate microglial cells with the production of $\text{TNF}\alpha$ and $\text{IL-1}\beta$ as well as superoxide. The molecular mechanisms involved are unknown but may involve cleavage of surface proteins on microglial cells such as receptors, cell-cell interaction proteins, cytokines and chemokines (reviewed by Kim and Hwang 2011).

Neuromelanin, a granular dark brown pigment, is produced in catecholaminergic neurons of the SNc and locus coeruleus and is possibly the product of reactions between oxidised catechols with a variety of nucleophiles, including thiols from glutathione and proteins (Götz et al., 2004). The function of neuromelanin in the pigmented neurons is unknown but it could play a protective role via attenuation of free radical damage by binding transition metals, particularly iron. In normal individuals, the neuromelanin-iron complex is found in

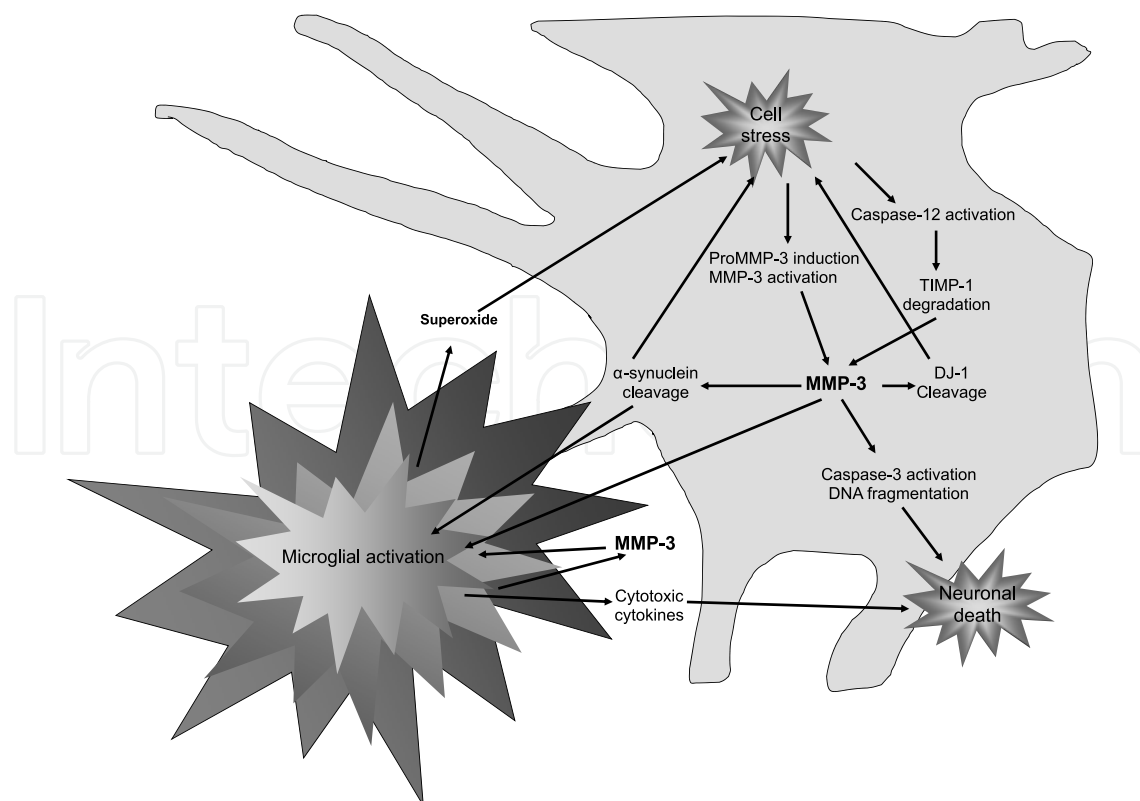


Fig. 5. Possible action of MMP-3 in neurodegeneration (adapted from Kim and Hwang, 2011)

both the SNc and locus coeruleus and increases linearly with age in the SNc. Whether the ability of the neurones to synthesis neuromelanin is impaired in PD patients is unknown, since it has been reported in some studies that the absolute concentration of nigral neuromelanin in individual neurons is less than 50% in PD with respect to age matched controls. However it is considered that when neuromelanin is released from the damaged neurons this will trigger microgliosis, microglial chemotaxis and microglial activation in PD with the subsequent release of neurotoxic mediators (reviewed in Crichton and Ward, 2006).

3.1 Stress

Stress will also have a major effect on microglial cells. Glucocorticoids are the major effector hormones of the stress system and act by binding to intracellular receptors within the cell, which are then translocated to the nucleus and act as regulators of gene expression. Generally female mammals show more robust behavioural and somatic responses to stress as well as more potent and inflammatory reactions than males (Chrousos, 2010). Stress hormones target glial cells, as well as neurons. (Jauregui-Huerta et al., 2010). Evidence that stress may contribute to the development of PD is unclear. However chronic stress will directly activate microglia as well as facilitating neuronal degeneration, which would activate microglia. Although psychological stress and glucocorticoids are reported to suppress immune function, (e.g. produce anti-inflammatory cytokines and reduce toxic radicals), possibly via glucocorticoid receptors on dopaminergic neurons, (Barcia et al., 2009), recent studies have indicated that glucocorticoids can enhance immune function in the brain (Reviewed by Jauregui-Huerta et al., 2010). This may be dependent upon the levels of glucocorticoids; i.e. high levels are pro-inflammatory while basal or low stress levels have traditional anti-inflammatory action. Such results may be important in that such stress-induced microglial activation may be involved in the progression of neurodegenerative diseases. Of the 13 epidemiological studies where the effect of stress has been studied as a possible contributory cause of PD, twelve of these studies were positive.

Serum factors, thrombin and immunoglobulins can initiate activation through protease-activated receptor 1 and Fc receptors, possibly after their passage across the BBB.

4. Polymorphisms of pro-and anti-inflammatory genes

Other contributory factors to the inflammation in PD could be functional DNA polymorphisms in some of the pro-inflammatory and anti-inflammatory cytokines which include TNF- α and IL-1 β genes (Wahner et al., 2007), IL-18 607C/A polymorphism and allele 1 (C) of IL-1 β (-511) (Arman et al., 2010), all of which are associated with an increased risk of PD in different populations. In contrast, the 2/2 (T/T) genotype of IL-1 β (-511) may protect individuals from PD (Arman et al., 2010). Genetic variations may also be present in the HLA (human leukocyte antigen) region, where there are numerous immune related genes, which would increase the risk of PD (Hamza et al., 2010; Wahner et al., 2007). The importance of TLR4 polymorphisms in modulating the inflammatory responses has been identified.

5. Apoptosis

Neurons and glia express cellular death signalling pathways which include CD95 (Fas)/CD95L, (FasL), TNF-TNFR-1, tumor necrosis factor- tumor necrosis factor receptor 1, and TNF-related apoptosis-inducing ligand (TRAIL), with which they are able to trigger apoptosis in T cells and other infiltrating cells (Griffiths et al., 2009). Glia also express pentraxins and

complement proteins. C1q, C3b and iC3b. . Hence, the rapid destruction of infiltrating T cells as well as injured neurons can be achieved by apoptosis in normal circumstances. Since apoptotic cells contain potentially neurotoxic proteins and cytokines their presence must be rapidly detected and cleared to prevent tissue damage. Such cells will express cell surface apoptotic cell-associated molecule patterns (ACAMPs) (that are comparable to PRPs), thereby identifying these cells for rapid removal from CNS to protect further damage. Failure to clear these apoptotic cells, which occurs in PD, will result in their accumulation within specific CNS tissues. Secondary necrosis of these cells will result in the release of their toxic contents thus enhancing tissue damage. Both CD47 and CD200 are expressed on microglia and are up-regulated during apoptosis, thereby inhibiting pro-inflammatory microglial cytokine expression. Apoptosis is a highly orchestrated form of cell death when a number of caspases are activated in a sequential manner. Inappropriate activation in the brain will have deleterious consequences. Apoptotic death is involved in the pathogenesis of PD.

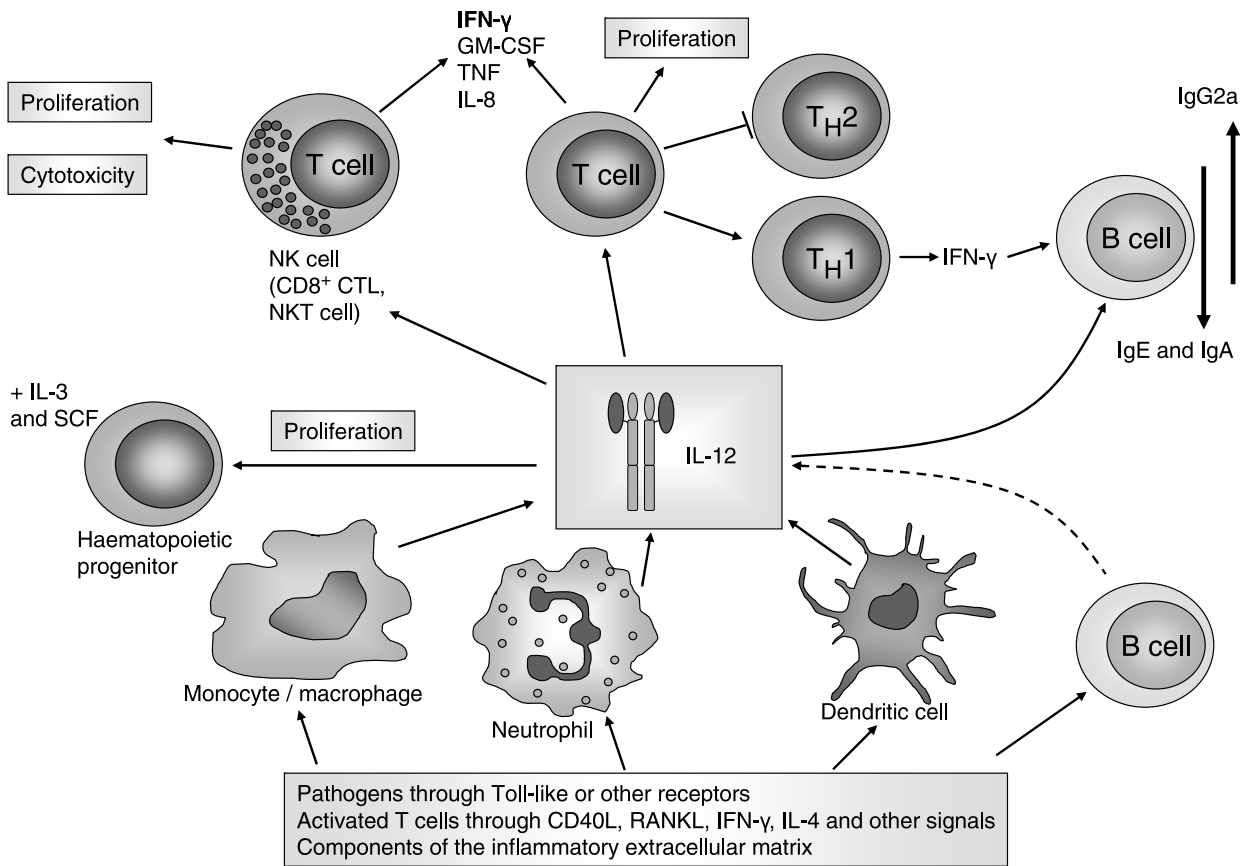


Fig. 6. Summary of the biology of IL-12 (adapted from Trinchieri, 2003)

6. Adaptive immunity and inflammation

Adaptive immunity is involved in the elimination of pathogens during the later phase of infection, (i.e. after activation of the innate immune system) and is elicited by B and T lymphocytes, which utilize immunoglobulins and T cell receptors, respectively, as antigen receptors to recognize “non self” molecules (**Figure 6**). These receptors are generated through DNA rearrangement and respond to a wide range of potential antigens. Adaptive immunity is acquired after a longer period in later life.

Lymphocytes, B-cells and T-cells are capable of responding rapidly to these specific insults/pathogens when the insult is again encountered. This mechanism allows a small number of genes to generate a large number of different antigen receptors which are expressed on each individual lymphocyte. This information will be inherited in all of the progeny, which includes memory B cells and memory T cells to give long-lived specific immunity. B cells play an important role in the humoral immune response while T-cells are intimately involved in cell-mediated immune responses. B cells are involved in the creation of antibodies that circulate in the blood and lymph which is known as humoral immunity. There are five types of antibodies, IgA, IgD, IgE, IgG and IgM. Upon activation, B cells produce antigen specific antibodies which in conjunction with the expression of unique B cell receptor (BCR), allow the identification of specific antigens.

6.1 CD8⁺ T lymphocytes and cytotoxicity

Naive cytotoxic T cells are activated when their T-cell receptor (TCR) strongly interacts with a peptide-bound MHC class I molecule. This affinity will depend on the type and orientation of the antigen/MHC complex. Once activated, the cytotoxic T cell undergoes a process known as clonal expansion in which it gains functionality, and divides rapidly, to produce a donor army of “armed”-effector cells which can travel throughout the body in search of cells bearing that unique MHC Class I + peptide. CD8 refers to a transmembrane glycoprotein which is a co-receptor for the T cell receptor. CD8 will bind to class I MHC protein.

6.2 CD4⁺ lymphocytes

CD4⁺ lymphocytes, (helper T cells), are immune response mediators which play an important role in establishing and maximizing the capabilities of the adaptive immune response. These cells have no cytotoxic or phagocytic activity but orchestrate the immune response by directing other cells to perform these tasks. CD4⁺ T helper cells can be induced to differentiate to specific lineages according to the local cytokine milieu, towards T helper type 1 Th1, Th2, Th17 and regulatory T cell (T_{reg}) phenotypes.

Microglial activation is propagated by T-cell releasing interferon- γ . This will sensitise the microglia by upregulating the expression of various immunoregulatory molecules including CD40 on their cell surfaces. Activation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling pathway plays a central role in this IFN- γ induced CD40 expression. Modulation of the JAK/STAT signalling pathway may suppress the microglial-mediated inflammation.

7. Adaptive immunity in PD

Extraneuronal nitrated α -synuclein is able to cross the BBB to the CSF where it will activate antigen presenting cells, (reviewed by Kosloski et al., 2010), i.e. naïve T cells. With appropriate co-stimulatory signals these cells will differentiate into T_{eff}s that will expand into different effector cell subtypes, e.g. Th1 and Th17 cells (Reviewed by Kosloski et al., 2010). Such cells will drive the disease processes towards a pro-inflammatory situation. Th1 cells express IL-2, IFN- γ and TNF α that are pro-inflammatory and will activate microglia. Th17 also elicits a pro-inflammatory effect (Kosloski et al., 2010) and will also secrete granzyme B, a cytolytic enzyme (Kebir et al., 2007). Th2 effectors release IL-4, IL-5 and IL-13 and support anti-inflammatory responses. In addition Th1, Th2 and Th17 help in the production of antibodies which specifically target modified proteins for their removal by microglia. Th1 and Th17 T_{eff}s are synthesised in the periphery and traverse the BBB to the

inflammatory foci of the nigrostriatum and identify the N- α -synuclein/major histocompatibility complex II which are presented by the antigen presenting microglia. The induction of Teffs will drive the microglia and the innate immune responses.

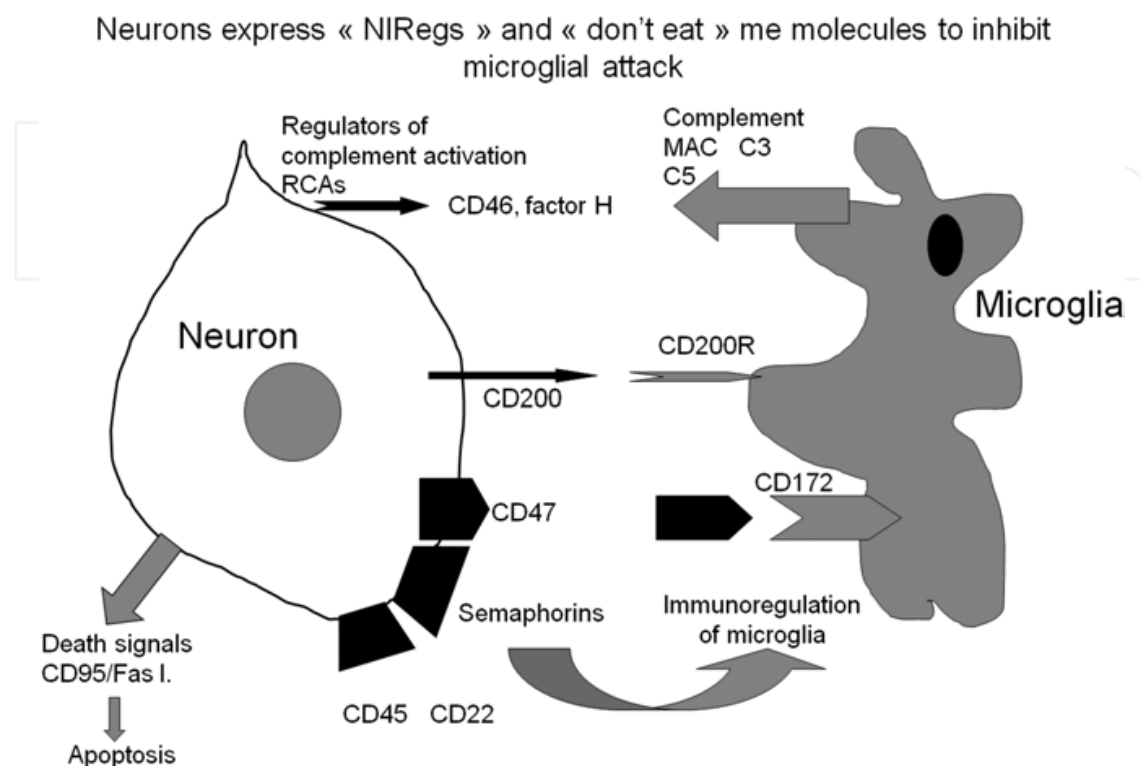


Fig. 7. Neurons express many 'self defence' proteins and receptors to prevent attack from microglia (adapted from Griffiths et al., 2010)

T cell infiltration is present in the CNS tissue of PD. Nitrated α -synuclein may activate peripheral leucocytes and mediate the adaptive immune system to potentiate microglial activation. Several changes in cellular and humoral immune responses are reported to occur in the peripheral immune system of PD patients, although no clear demonstration of leucocyte involvement at the site of the neuronal damage has been reported (Brochard et al., 2009). However McGeer et al., (1998) identified cytotoxic T cells in the SNc of one PD patient while Hunot et al (1999) showed a dramatic increase of IFN- γ positive cells in brains of PD patients indicating that T cells mobilisation could be involved in the nigrostriatal injury in PD. In one further study by Brochard et al., (2009), higher densities of CD8⁺ and CD4⁺ T cell were present post mortem in PD brains. This may indicate that there are changes in the function of the blood brain barrier and that peripheral cells are entering the brain parenchyma. In a recent study, (Castellani et al., 2011) identified a subunit of CD3, part of the T receptor complex (TRC) on mature T cells, in Lewy bodies in PD. This subunit of CD3 has also been shown to be involved in dendritic outgrowth and synaptic formation thus raising the possibility that CD3 dysregulation as a pathogenic factor in PD.

8. Anti-inflammatory systems to regulate microglia activation

There are several anti-inflammatory systems that play a role in regulating microglia activation which include CD200/CD200 receptor, vitamin D receptor, peroxisome proliferator-activated receptors and soluble receptor for advanced glycation end products (Lue et al., 2020)

8.1 CD200/CD200 receptor

CD200 is a highly glycosylated protein. Its expression is primarily located to neurons and oligodendrocytes in human brain although both astrocytes and brain endothelial cells also express CD200 (Koning et al., 2007; Walker et al., 2009). With increasing age a loss of mRNA CD200 expression is reported in cells of rodents (Frank et al., 2006) which may also occur in humans. CD200R expression is found on many inflammatory cells which include macrophages, neutrophils, microglia, granulocytes, T lymphocytes, astrocytes and oligodendrocytes (Rijkers et al., 2008). The only known function for CD200 is to bind to CD200R. This ensures that the microglia remain in the resting state, **Figure 8**. The binding at the N-terminal of each of these molecules activates specific anti-inflammatory signalling pathways in CD200R expressing cells, thereby down regulating the pro-inflammatory response (Hatherley and Barclay, 2004). Loss of CD200, which is evident in PD brain regions where there is a loss of neurons, will induce an accelerated microglia response (Hoek et al., 2000). In addition, the activation of the extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38 mitogen activated protein kinase (MAPK) pathways will be inhibited by such binding (Zhang et al., 2004). Treatment of microglia and macrophages with IL-4 and IL-13 significantly increased expression of CD200R, *in vitro*. However expression of these cytokines was not generally detectable in brain (Walker et al., 2009). These anti-inflammatory cytokines bind to the same receptor complex and can activate the STAT-6 transcription factor. Activation of STAT-6 occurs in IL-4 stimulated human brain microglia which correlates with increased expression of CD200R. IL-4 exerts a powerful control over CD200 expression and hence modifies microglial activation. Therefore enhancing levels of IL-4 in the brain would be advantageous. Both statins and Vitamin D(3) will enhance IL-4 levels and thereby enhance an anti-inflammatory effect.

8.2 Vitamin D receptor (VDR)

Vitamin D3 plays a central role in immunity by a) modulating the production of several neurotrophins, (b) upregulating IL-4, and c) inhibiting the differentiation and survival of dendritic cells (Fernandes de Abreu, et al., 2009). Deficiency of vitamin D3 may be associated with increased CNS diseases including PD (reviewed by Annweiler et al., 2009). The cellular receptor for vitamin D3, the vitamin D3 receptor (VDR), (nuclear receptor subfamily, group 1, member 1 (NR111) and calcitriol receptor is a member of the nuclear receptor family of transcription factors. Upon activation by vitamin D, the VDR forms a heterodimer with the retinoid-X-receptors which binds to hormone responsive elements on DNA, which causes an increased expression or repression of specific genes. Indirect evidence has suggested that PD have lower serum vitamin D than age matched controls (Sato et al., 2005). In a longitudinal study of 3000 participants in Finland, higher vitamin D levels were associated with a reduced risk of PD (Knekt et al., 2010).

8.3 Peroxisome proliferators activated receptors

The peroxisome proliferator-activated receptors, PPARs, belong to a superfamily of nuclear hormone receptors (**Figure 8**). Their main function is to regulate glucose and lipid metabolism and their subsequent storage. However, they also play a key role in the regulation of immune and inflammatory responses. PPARs can stimulate gene expression through binding to peroxisome-proliferator response elements, which are present in the promoter regions of target genes. The PPAR subfamily is comprised of three isoforms, PPAR- α , PPAR- β/δ and PPAR- γ . PPAR are activated by small lipophilic compounds and

form heterodimers with the retinoid receptor- α (RXR) in the cytoplasm for full activation. Specific binding of PPAR onto DNA sequences leads to the activation of gene cascades involved in several biological processes (Reviewed by Chaturvedi and Beal, 2008). In the absence of ligands, PPAR and RXR heterodimers bind to co-repressor complexes and suppress gene transcription (Reviewed by Chaturvedi and Beal, 2008). PPARs also downgrade the production of MMPs, known activators of microglia and PPAR- γ agonists have been shown to be neuroprotective in a number of PD models.

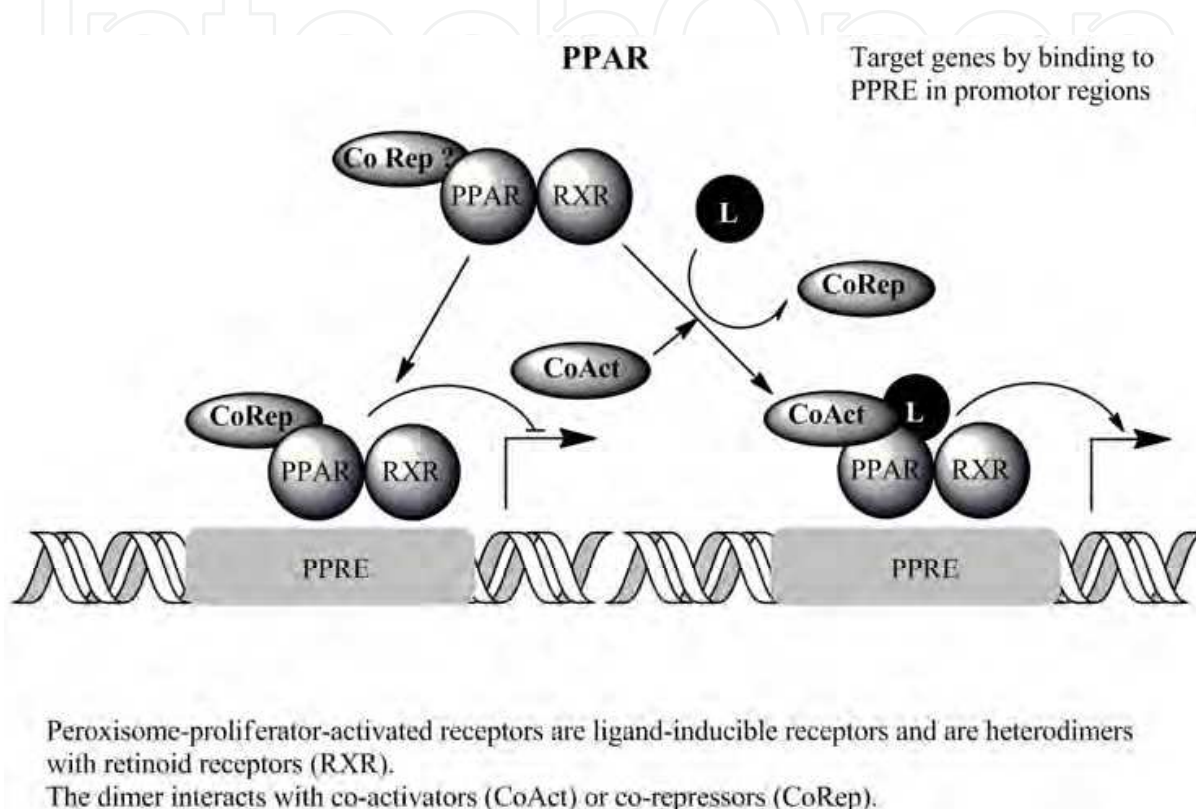


Fig. 8. Schematic representation of the PPAR signalling pathway (Adapted from Michalik et al., 2004)

9. Role of iron in inflammation in PD

There is an increased burden of iron, approximately 2 fold, compared to controls, in specific brain regions, the SNc and lateral globus pallidus of PD brains which will enhance oxidative stress (Gotz et al., 2004). H-ferritin rather than L-ferritin is present in the iron loaded SNc and lateral pallidus of PD brain (Dexter, et al., 1990) with large amounts of iron being sequestered into neuromelanin in dopaminergic neurons. Furthermore, since the SNc has a relatively high metabolic rate, with a high content of dopamine, neuromelanin, polyunsaturated fatty acids and iron, but low antioxidant protection, e.g. reduced glutathione (Sian et al., 1994) oxidative stress will be enhanced. Both reactive oxygen and nitrogen intermediates will contribute to the demise of the dopaminergic neurons, leading to the formation of lipid peroxidation products, as well as protein carbonyls and DNA damage (Alam et al., 1997). In addition, ROS, generated as a result of mitochondrial malfunction, will contribute to this toxicity. The etiology of this enhanced brain iron content may be attributable to a variety of factors which include changes

in iron release mechanisms across the blood brain barrier, BBB, or perhaps more likely, a mis-regulation of iron homeostatic control in the SNc.

The control of iron homeostasis within microglia remains undefined. It is of interest that both microglia and iron deposits co-accumulate at the site of damage in PD. Whether these accumulations are a cause or effect of the disease is currently unknown. In our recent study (Ward et al., 2007) mRNA was isolated from two regions of Parkinson's brain, the SNc and the cortex, and the expression of a number of iron genes quantitated and compared with those from control post mortem material. A significant number of genes were specifically up-regulated in the substantia nigra in comparison to the cortex in the PD brains as well as controls, **Table 2**. Such up-regulation of both transferrin and transferrin receptor2 in other cell types is associated with iron deficiency, and inflammation, respectively. The high iron content of the SNc might have been expected to diminish IRP1 and IRP2 activity. However IRP-1 expression did not alter significantly whilst IRP2, which dominates post-transcriptional regulation of brain iron metabolism was up-regulated. A previous study, (Faucheux et al., 2002) reported no alteration of IRP-1 in SNc of Parkinsonian brain. The increased mRNA expression of ferroportin in SN might indicate an elevated flux of iron from certain cell types within the SNc.

Descriptor	Gene	SnM p-value	Sni	Cortex
UPREGULATED				
IRP-binding protein 1	IRP1	ns	ns	ns
IRP-binding protein 2	IRP2	0.025	ns	ns
Transferrin	Tf	0.0001	0.0030	ns
Transferrin receptor 2	TfR2	ns	0.0017	ns
Transferrin receptor 2	TfR2	ns	0.0184	ns
Ferritin H	FTH1	0.0019	ns	ns
Ferritin H pseudogene 1	FTHP1	0.0010	0.0348	ns
Ferritin L	FTL	0.0291	ns	ns
FerritinL	FTL	0.0335	ns	ns
Ferritin L	FTL	ns	0.006	ns
Caeruloplasmin	Cp	0.0276	0.0276	ns
Caeruloplasmin	Cp	ns	0.0343	ns
Caeruloplasmin	Cp	ns	0.0336	ns
Hephastin	HEPH	ns	0.009	ns
Haemochromatosis	HFE	0.0416	0.0005	ns
Haemochromatosis	HFE	ns	0.0111	ns
Haemochromatosis	HFE	ns	0.0295	ns
Haemochromatosis	HFE	ns	0.0039	ns
Ferroportin	FPN1	0.0192	ns	ns
Ferroportin	FPN1	0.0353	ns	ns
Solutecarrier family11	SLC11A2	ns	ns	0.0291
DOWNREGULATED				
Ferrochetalase		0.006	0.0223	ns
Sideroflexin 1		0.006	0.0314	ns
Friedreich ataxia		0.031	ns	ns

Table 2. Activated microglia secrete a number of factors which include cytokines, chemokines and receptors

10. Role of blood brain barrier in inflammation

The exact role played by the blood brain barrier (BBB) in excluding and permitting various molecules to cross the membrane remains an enigma. In early studies, molecular size was considered to be an important factor. However later studies have identified that passive diffusion across the blood brain barrier is very slow and that various transporters, solute carriers, as well as transcytosis, play important roles in determining whether molecules traverse the BBB. Furthermore endothelial astrocytes and neurons which are in contact with the cells of the BBB will influence intra and intercellular signalling (Neuwelt et al., 2011). The function of the BBB may be altered by inflammation in the periphery with inflammatory mediators inducing a significant paracellular leak. Immune cells are able to penetrate BBB, either at the endothelial BBB or the epithelial blood-CSF barrier. Interaction of endothelial cells with extracellular matrix will induce cross talk with adjacent cells which are prerequisite for barrier function. For example $\alpha 4\beta 1$ -integrin/VCAM-1 is involved in leucocyte interaction with BBB. Inflammation and generation of ROS and RNS can acutely disrupt BBB at tight junction. Stress related pathways target nuclear transcription factors to increase P-glycoprotein expression in blood capillaries. There is altered expression of p-glycoprotein at BBB in PD. Therefore BBB function may contribute to neuro-inflammation via deregulated entry of antigen-specific T cells, via compromised removal of toxic products of neuronal damage and death and lead to disease progression via signalling of systemic inflammation. It remains unclear whether there is BBB leakage in PD patients. Polymorphism in the P-glycoprotein drug transporter MDR1 gene association and ABCB1 gene encoding the P-glycoprotein may alter the properties of the BBB in PD patients (Reviewed by Neuwelt et al., 2011).

11. Inflammation in the periphery

Possible biofluids which can be used in the search for pertinent PD biomarkers are the cerebrospinal fluid, plasma and urine. It would be advantageous clearly to identify markers which precede the degeneration of nigrostriatal dopaminergic neurons. For example it is known that an impaired sense of smell is prevalent prior to and during the clinical motor stages of PD. Odour discrimination performance strongly correlates with risk of future PD (Berendse and Ponsen, 2009). In addition reduced striatal dopamine transporter SPECT imaging was also identified in subjects, who later developed PD. Biomarkers which correlated with these early physical symptoms would be of paramount important for early therapeutic intervention. In a small study of 84 subjects, (Chen et al., 2008), plasma inflammatory biomarkers were assessed approximately 4 years before PD diagnosis, IL-6 was associated with a greater risk of PD. Other inflammatory markers such as C-reactive protein, fibrinogen, and TNF- α were not related with risk. In contrast, analysis of serum and cerebrospinal fluid from PD patients which have active and progressive PD, it was not surprising that increased levels of the inflammatory cytokines TNF α , IL-1 β , IL-2, IL-4, IL-6 and interferon γ were observed (Bacia et al., 2009). Similarly, increased oxidative damage is involved in the progression of PD and plasma levels of F(2)-Isoprostanes, hydroxyeicosatetraenoic acid products, 7 beta and 27-hydroxycholesterol, 7 ketocholesterol, F(4)-neuroprostanes and urinary 8-hydroxy-2'-deoxyguanosine were elevated in PD patients while plasma levels of phospholipase A(2) and platelet activating factor acetylhydrolase activities were lower (Seef et al., 2010).

CSF may be the most promising biological fluid since it is in closer contact with degenerating neurons. The assay of both alpha-synuclein and DJ-1 have been shown to be good biomarkers for PD but larger clinical trials as to their potential use are needed. Although some studies have advocated the assay of a pattern of inflammatory cytokines, further investigations are required to ascertain their specificity for PD.

Plasma homocysteine was increased in PD patients (Obeid et al., 2009) while platelet levels of amyloid precursor proteins and alpha synuclein may be pertinent markers of methylation. In addition various polymorphisms have been identified in the genes of TNF α and its receptor, as well as IL-1 α and IL-1 β (Wahner et al., 2007). All of these studies have been on small numbers of PD patients. However other studies have not confirmed the associations of such polymorphisms with PD disease (Reviewed by Hirsch and Hunot, 2009) which may indicate that such polymorphisms are involved in susceptibility to the causative agent of PD. More importantly such polymorphisms may reflect the basal levels of the inflammatory status of an individual or reflect the ability of phagocytic cells to respond to an inflammatory stimulus.

Various changes in antibodies have been identified in the serum of PD patients although these have not been confirmed in all studies (reviewed by Hirsch and Hunot, 2009). Increased numbers of circulating CD4⁺ bright and CD8⁺ dull lymphocytes are detectable in the serum of PD patients (Hisanaga et al., 2001). Since the counts of these lymphocytes increase after viral infection, this could indicate that viral infections contribute to the pathogenesis of PD.

12. Therapeutic aspects

There have been some discussions as to whether improvements in the ability of the immune system to respond to the inflammatory turmoil maybe of importance in preventing the progression of PD. Probiotics, are dietary supplements which contain beneficial bacteria, (lactobacillus and bifidobacterium), or yeast. They are administered in different quantities to allow for colon colonization. They help by stimulating health promoting flora as well as suppressing pathogenic colonisation and disease. It is claimed that probiotics will strengthen the immune system to combat allergies, stress and possibly neurodegenerative diseases (Saraf et al., 2010).

12.1 Anti-inflammatory agents

Some epidemiological studies have indicated that people who regularly use anti-inflammatory drugs have less risk of developing clinical PD (Chen et al 2003., Chen., 2005), although this has not been confirmed in other studies (Ton et al., 2006; Bornebroek et al., 2007; Hancock et al., 2007). Anti-inflammatory drugs may retard the progression of the degeneration although it remains to be elucidated whether their use would be an additional therapy in diagnosed PD patients. Inhibition of inflammation is associated with reduced neuronal impairment in various PD models (Gao et al., 2003; Wu et al., 2003) as discussed below.

Non-steroidal anti-inflammatory (NSAI) drugs act by inhibiting the enzyme cyclooxygenase COX-1 and COX-2. While aspirin will inhibit both COX-1 and COX-2, ibuprofen will inhibit COX-2 only. COX-2 is specifically involved in dopaminergic degeneration. COX-2 inhibitors have been demonstrated to specifically inhibit microglia activation. NSAI may be effective in decreasing the incidence of PD which has been associated with the COX-inhibiting effect

of these compounds (Chen et al., 2005). Minocycline may be effective in delaying PD progression by suppressing the formation of IL-1 β and the activation of NADPH-oxidase and iNOS which are potent activators of microglia (NINDS 2006; Couzin 2007). The presence of polymorphisms of pro-inflammatory genes such as COX-2 genes may provide a genetic predisposition to initiate microglial activation.

12.2 Antioxidants

Antioxidants may reduce the progression of the neurodegenerative process. Lipoic acid is a universal antioxidants. Lipoic acid in its reduced form dihydrolipoic acid is active against ROS and will reduce oxidative stress. (De Araujo et al., 2011). However peripherally administered antioxidant will need to be targeted to specific regions of the brain where oxidative stress occurs.

12.3 Vitamins and mineral

Micronutrients such as the Vitamins A, B₆, B₁₂, C, D and E, folic acid as well as iron, zinc, copper and selenium, are involved in the synergy to support the protective properties of the immune system and most are also essential for antibody production (Maggini et al., 2007). Supplementation with these micronutrients may enhance immunity.

12.4 Steroid hormones

Steroid hormones, such as 17 beta oestradiol or progesterone protect against dopaminergic degeneration which may explain why woman are less affected by PD. In addition oestrogens may reduce inflammatory processes in the brain (Reviewed by Barcia et al., 2009) diminishing glial cell activation around dopaminergic neurons possibly mediated by differential expression of oestrogen receptors on glial cells and neurons (Reviewed by Barcia et al., 2009).

12.5 Flavonoids

Flavonoids, a group of phenolic phytochemicals are abundant in various spices, vegetables and fruit. Several medicinal properties have been ascribed to flavonoids which include antioxidants, anti-inflammatory and anti carcinogenic. Apigenin and its phase I metabolite, luteolin reduce CD40 and CD40L expression on dendritic cells and basophils. In our recent investigation of apigenin and luteolin in cultured microglia it was demonstrated that both of these compounds significantly reduced CD40 expression induced by IFN- γ . This was paralleled by significant decreases in the release of pro-inflammatory cytokines IL-6 and TNF α by microglia. Such changes were due to inactivation of STAT1 (Datla et al., 2001, 2007; Zbarsky et al., 2005).

12.6 Taurine and taurine prodrugs

In our recent studies we have shown that taurine has an anti-inflammatory action by stabilisation of IkappaB α in macrophages and microglia (Ward et al., 2011). This in turn will reduce NFkappaB translocation to the nucleus and will prevent the release of pro-inflammatory cytokines. In earlier animal studies the protective effect of taurine in the 6-hydroxy dopamine model was reported (Ward et al., 2006). In the later studies, prodrugs of taurine have been developed, notably ethane- β -sultam, which reduce microglial activation in the brain of an animal model of neurodegeneration (Ward, Della Corte, Dexter unpublished data).

12.7 Iron chelators

The iron content of the SNc increases in the brains of PD patients and is associated with the progression of the inflammatory process. Hence, its chelation may prevent the progression of the disease. Two clinically used iron chelators, namely the hexadentate, deferrioxamine and the tridentate chelator deferasirox have been investigated for their efficacy to induce neuroprotection in the 6-hydroxy dopamine (6-OHDA) animal model of PD. Acute administration of deferrioxamine, 0.4 mM or deferasirox, 1 mM, via a microdialysis probe into the striatum immediately prior to a dose of 6-OHDA, prevented the generation of hydroxyl radicals, as well as reducing bio-available iron. Intraperitoneal injection of the iron chelators, deferasirox, 20 mg/kg or deferrioxamine, 30 mg/kg or deferiprone 10mg/kg, to the 6-OHDA rat model, significantly attenuated the loss of tyrosine hydroxylase positive cells as well as elevating dopamine content in the lesioned striatum (Dexter et al., 2010). Such results would confirm that the administration of these chelators show therapeutic efficacy and should be considered to be an additional therapy for the treatment of PD. Clinical trials of deferiprone are now underway in a group of drug-naïve PD patients.

12.8 MMP-3 inhibitors

The development of selective MMP-3 inhibitors has proved difficult. It is unlikely that relatively large peptide based inhibitors of MMP-3 would cross BBB. Doxycycline, a tetracycline derivative that crosses the BBB can down regulate cell stress induced MMP-3 expression and release and can therefore attenuate apoptosis in dopaminergic neurons (Cho et al., 2009). Minocycline protection of neurones from a variety of insults may in part be due to down regulation of MMP-3. However early clinical trials in PD patients were stopped because of unwanted side effects (NINDS NET-PD Investigators 2008). Preliminary studies of ghrelin, glycitein and exendin-4 have also shown down regulation of MMP-3 expression (reviewed by Kim and Hwang, 2011).

12.9 PPAR modifications

Several non-steroidal anti-inflammatory drugs bind to PPAR- α and PPAR- γ , thereby activating their receptors. PPAR regulate the transcriptional activity of several transcription factors which include NFkappaB, the signal transducer factor-1 (STAT) and the activating transcription factor-1, ATF-1 and ATF-4. PPAR function by competing with NFkappaB for binding to the overlapping series of co-activators, i.e. cAMP-response element-binding protein (CREB), and inhibiting the NFkB mediated inflammatory response. PPAR also directly interacts with p65/p50/IkBa suppressing the DNA binding activity of NFkB. PPAR also inhibit NFkB and AP-1 signal-dependent transcriptional activation of inflammatory genes by transrepression (Reviewed by Chaturvedi and Beal, 2008). Modulation of iNOS and cyclooxygenase may also occur. PPAR may play a role in improving mitochondrial function. The neuro-protective role of PPAR agonists have been evaluated in PD patients. Agonists such as pioglitazone and rosiglitazone, may be able to protect against oxidative stress, apoptosis and inflammation in CNS (Reviewed by Chaturvedi and Beal, 2008).

13. Inflammation in animal models of PD

Activation of microglia has been identified in the SNc and /or striatum in various animal models of PD, which include the MPTP and lipopolysaccharides models (reviewed by Marinova-Mutafchieva et al., 2009). In addition, in the medial forebrain bundle axotomised

model, brain activation of microglia precedes neuronal loss (Gao et al., 2003). In the 6-hydroxy dopamine models significant microglia activation was evident 48h after its administration as well as NADPH- derived free radicals prior to dopamine cell death in the SNc. In our recent studies unilateral injection of 6-OHDA into the medial forebrain bundle, activation of microglia occurred rapidly, which selectively adhered to degenerating axons dendrites and apoptotic dopamine neurons in the SNc after 7 days.(Dexter et al 2011). After this time, there was a progressive loss of tyrosine hydroxylase positive neurons. These results indicated that microglia activation precedes dopamine neuronal cell loss. Furthermore neurons undergoing degeneration may be removed prematurely by microglia phagocytosis. (Marinova-Mutafchieva et al., 2009). In vitro it has also been shown that the toxicity of LPS to immortalised dopaminergic neurons was evident only when microglia were present in the cell culture (Gao et al., 2003). These results clearly indicate that activated microglia play an important role in the early stage of the disease pathogenesis.

This review has confirmed that in PD there is a persistent and progressive inflammation both in the periphery and brain which is caused by changes in both the innate and adaptive immune systems which fuel the degeneration. The factors involved in the initiation of this cycle remains unknown. Although therapeutic intervention may diminish such inflammatory pathways, the goal for future researchers will be to identify the cause of such perturbations. Only then will there be the opportunity to develop new drugs which will cure PD.

14. References

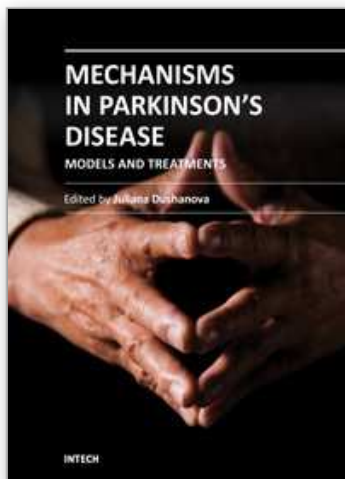
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Parkinson's disease (PD) results primarily from the death of dopaminergic neurons in the substantia nigra. Current PD medications treat symptoms; none halt or retard dopaminergic neuron degeneration. The main obstacle to developing neuroprotective therapies is a limited understanding of the key molecular mechanisms that provoke neurodegeneration. The discovery of PD genes has led to the hypothesis that misfolding of proteins and dysfunction of the ubiquitin-proteasome pathway are pivotal to PD pathogenesis. Previously implicated culprits in PD neurodegeneration, mitochondrial dysfunction, and oxidative stress may also act in part by causing the accumulation of misfolded proteins, in addition to producing other deleterious events in dopaminergic neurons. Neurotoxin-based models have been important in elucidating the molecular cascade of cell death in dopaminergic neurons. PD models based on the manipulation of PD genes should prove valuable in elucidating important aspects of the disease, such as selective vulnerability of substantia nigra dopaminergic neurons to the degenerative process.

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