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Cellular and molecular pathophysiology in the progression of Parkinson's disease

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder etiologically linked to the loss of substantia nigra (SN) dopaminergic neurons in the mid-brain. The etiopathology of sporadic PD is still unclear; however, the interaction of extrinsic and intrinsic factors may play a critical role in the onset and progression of the disease. Studies in animal models and human post-mortem tissue have identified distinct cellular and molecular changes in the diseased brain, suggesting complex interactions between different glial cell types and various molecular pathways. Small changes in the expression of specific genes in a single pathway or cell type possibly influence others at the cellular and system levels. These molecular and cellular signatures like neuroinflammation, oxidative stress, and autophagy have been observed in PD patients' brain tissue. While the etiopathology of PD is still poorly understood, the interplay between glial cells and molecular events may play a crucial role in disease onset and progression.

Keywords

Autophagy; Neuroinflammation; Neuron; Oxidative damage; Parkinson's disease; Substantia nigra

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease, clinically defined as a movement disorder. The pathological hallmarks of PD are the degeneration of dopamine-producing neurons in the ventral midbrain substantia nigra (SN) and associated widespread intraneuronal α-synuclein aggregation in Lewy bodies (Braak et al. 2003; Maiti et al. 2017). As the disease progresses, the loss of SN dopaminergic neurons results in the typical motor symptoms, such as bradykinesia, rigidity, impaired postural balance, and a characteristic resting tremor. PD patients develop dementia as the disease progresses (Goetz 2011; Moustafa et al. 2016). In addition, prodromal symptoms have been reported by PD patients years before the onset of disease. Some of these signs include constipation, insomnia, mood disorders, depression and anxiety (Mahlknecht et al. 2015). The etiopathology of sporadic PD is still unknown; however, studies suggest that the interaction of extrinsic and intrinsic factors, such as exposure to environmental toxins and specific immune responses, may trigger disease onset (Sulzer 2007). Moreover, according to Braak's hypothesis, the idiopathic incidence of PD may originate outside the CNS (most probably in the enteric nervous system) while "the stereotypic topographic expansion pattern of the lesions may resemble that of a falling row of dominos" (Braak et al. 2003). The α-synuclein aggregation has recently been demonstrated to begin in the enteric nervous system and propagates to the brain via the vagus nerve (Kim et al. 2019).

PD brain analysis suggests that multiple pathways may be responsible for the death of nigral neurons. An electron microscopic observation of PD brain samples suggested apoptotic, necrotic, and autophagic cell death of nigral dopaminergic neurons (Anglade et al. 1997). The presence of an autophagosomal marker, the microtubule-associated protein 1A/1B-light chain 3 (LC3), in the Lewy bodies of the PD patients supports the active role of autophagy in this disease (Tanji et al. 2013). Beclin-1, an autophagy regulator protein, is also increased in PD brains (Spencer et al. 2009). Additionally, the aggregated form of α-synuclein, which is a predominant component of Lewy bodies, may be the result of dysfunctional autophagy (Arotcarena et al. 2019). Interestingly, in the post-mortem PD brain, observed microglial activation is correlated with the presence of this aggregated α-synuclein form (Croisier et al. 2005). The active participation of inflammation in PD is seen by the presence of cytokines in PD brains (Nagatsu et al. 2000) and the presence of CD4 + T cells in PD animal models (Haque et al. 2020; Samantaray et al. 2015). Aggregated α-synuclein also induces reactive oxygen species (ROS) production in the cells (Reeve et al. 2015), and oxidative stress can exacerbate the α-synuclein aggregation (Glick et al. 2010; Scudamore and Ciossek 2018). Thus, the detection of multiple deleterious pathways in PD brains and associated animal models suggest that these pathways may interact with each other in disease initiation and progression.

Therefore, recent studies have focused on ascertaining which cellular pathways lead to the onset of pathological changes in specific brain regions. Experimental studies in animal models and human post-mortem tissues have recognized some key players in the progression of PD. Therefore, one specific event may be required to initiate cell death (primary pathway), which leads to the involvement of other secondary pathways, much like the "falling row of dominos". Significant participants in the central nervous system (CNS)

include neurons, astrocytes, microglia, oligodendrocytes, vessel-associated cells, resident innate immune cells, and immune cells from the peripheral system. A complex network of crosstalk between these cells together with cytokines and chemokines supports function of the normal brain. However, any subtle changes of extrinsic or intrinsic factors in the surrounding environment may disrupt regular interaction. Increasing numbers of studies are suggesting the critical role of neuroinflammation in neurodegenerative diseases. There is a delicate molecular balance during the neuroinflammatory process, and glial cells can help prevent or repair the damage caused by initial insults (Fig. 1). Activation of glial cells together with signals from infiltrating immune cells can contribute to pathophysiological changes in neurodegenerative diseases. Thus, it is becoming increasingly clear that a complex communication network between neurons, glia, and immune cells may play a detrimental role in the disease process.

Beyond sporadic PD, there are known genetic risk factors involved in initiating Parkinsonian progression (Nuytemans et al. 2010). Well defined mutations include: Leucine-Rich Repeat Kinase 2 (LRRK2), Protein DJ-1 (DJ-1), α-synuclein (SNCA), Ubiquitin C-Terminal Hydrolase L1 (UCHL1), PTEN-Induced Putative Kinase 1 (PINK1), and Parkin (PRKN) (Abeliovich and Gitler 2016; Jin and Youle 2012; Jones 2010; Liu et al. 2017; Marongiu et al. 2009; Nuytemans et al. 2010). Familial PD (autosomal dominant or recessive inheritance of the genes) patients represent only 5–10 % of PD cases. Moreover, the disease onset and progression are heterogeneous (Martinez and Peplow 2017), suggesting several subtypes of PD may exist. The critical role of mitochondria in PD is demonstrated in these known mutations, which result in mitochondrial damage and ROS formation (Klein and Westenberger 2012; Selvaraj and Piramanayagam 2019). As discussed below, animal models of PD with these mutations are valuable to aid understanding of the underlying cellular and molecular disease mechanism(s) in other non-familial cases.

Neuroinflammation

Microglia

The role of microglia in neuroinflammation has been studied in neurodegenerative diseases such as PD, Amyotrophic lateral sclerosis (ALS), and Alzheimer’s disease (AD) due to their activated presence at lesion sites in diseased patients’ brains (McGeer et al. 1988a, b). McGeer and collaborators (McGeer et al. 1988a, b) detected reactive microglia in the SN of PD and AD patients; they suggested that the presence of microglia is a sensitive indicator of pathological changes in these neurodegenerative disorders. Histological evaluation of PD patient brains also detected activated microglia and reactive astrocytes (Kam et al. 2020), suggesting neuroinflammation may be a critical factor in the disease process (Lecours et al. 2018; Long-Smith et al. 2009).

Microglia and astrocytes are known to play crucial roles in maintaining brain homeostasis (Barres 2008; Colombo and Farina 2016; Gertig and Hanisch 2014; Heithoff et al. 2021; Khakh and Sofroniew 2015; Linnerbauer et al. 2020; Paolicelli et al. 2011); alterations in glial cell activation status caused by peripheral events may eventually lead to pathological changes in the CNS. Microglia are resident innate immune cells (initial responders in the CNS) derived from the primitive hematopoietic progenitors in the yolk sac on embryonic

day 8; by embryonic day 10.5, these cells colonize the developing brain (Alliot et al. 1999). Later, microglia maintain their region-specific density by self-renewal (Ajami et al. 2007; Li and Barres 2018). Microglia appear in the brain before other glial cells (astrocytes and oligodendrocytes) and neurons (Kriegstein and Alvarez-Buylla 2009), suggesting that they could play essential functions in the brain during development. They also perform immune surveillance (Nimmerjahn et al. 2005) and respond to CNS pathogens and injuries. Studies have shown that microglia actively prune synapses in the developing brain, playing a prominent role in maintaining brain homeostasis during development (Weinhard et al. 2018). A recent study by Socodato and collaborators observed synaptic pruning in adult mice following alcohol intoxication (Socodato et al. 2020), leading to anxiety-like behavior. Similarly, the regulation of neurogenesis in the adult hippocampus indicates microglial involvement in maintaining brain homeostasis later in life (De Lucia et al. 2016; Diaz-Aparicio et al. 2020; Frost and Schafer 2016; Sato 2015).

Associated with the diverse array of neurons (Lein et al. 2007), microglial populations in the brain are also heterogeneous (Li et al. 2019), and the SN (characteristically affected in PD) is densely populated by microglia (Lawson et al. 1990). Like neurons, microglial populations also demonstrate distinct region-dependent molecular identity (Grabert et al. 2016) suggesting distinct functions in different brain areas. Age and chronic stress are believed to induce morphological and functional changes (Lecours et al. 2018). Microglia and estradiol actively participate in the pre-optic area during the critical perinatal development period for sexual differentiation in male mice (Lenz et al. 2013). Transcriptome analyses in young adult male/female mice revealed the differentially expressed genes in microglia isolated from female mice compared to male mice (Villa et al. 2018). This study found that genes associated with inflammatory processes are more highly expressed in male mice. Contrary to this, females differentially expressed genes associated with inhibiting inflammatory responses and more robust repair mechanisms. The transcription factor driving the differentially expressed genes in microglia is the nuclear factor κB (NF-κB). This sex-specific difference highlights the role of microglia since PD is more prevalent in males than females by a 2:1 ratio, respectively (Cerri et al. 2019; Hirsch et al. 2016; Picillo et al. 2017). Recent studies have likewise demonstrated neuroprotective properties of low-dose estrogen treatment in rats following spinal cord injury (Cox et al. 2021). Wu and collaborators demonstrated sex- and age-specific differences in SN microglia density in mice (Wu et al. 2016). Moreover, they showed the association of activated microglia with SN dopaminergic neurons, where the high density of activated microglia leads to fewer SN neurons. Since microglia express estrogen receptors (Sierra et al. 2008; Thakkar et al. 2018; Wu et al. 2016), neuroprotective estrogen may inhibit inflammatory responses in microglia reducing the incidence of PD in women.

Regional variations in microglial phenotypes and functions indicate they are versatile cell types, regulated in part by the local microenvironment (De Biase et al. 2017; Lenz et al. 2013). The transcriptome analysis by Villa et al. (Villa et al. 2018) showed that in addition to having a neuroprotective phenotype, microglia from female mice express fewer inflammatory markers than those from male mice. In addition, De Biase et al. (De Biase et al. 2017) demonstrated a regional variation in microglial phenotypes in basal ganglia associated with local factors. A dense population of microglia in SN (Kim et al. 2000) may

predispose this brain region to immune challenge. Since basal ganglia are specifically affected in PD, this variation in microglial phenotype requires more attention to further evaluate its functional role in normal and disease states.

Microglial activity is commonly categorized by proinflammatory (M1) and antiinflammatory (M2) phenotypical characteristics (Fig. 2a). The presence of neurotoxic M1 microglia at the site of neurodegeneration suggests this phenotype may have replaced the neuroprotective M2-type microglia, or transformed from M2 to M1 during the disease process (Tang and Le 2016). Since the presence of local cues plays a critical role in regulating microglial phenotypes, the presence of aggregated α-synuclein, amyloid beta (Aβ) or other unknown stimuli may promote specific microglial phenotypical expression (Ferreira and Romero-Ramos 2018; Sala Frigerio et al. 2019). Moreover, the high density of microglia in SN may produce an abundance of proinflammatory cytokines/chemokines, leading to the degeneration of nigral neurons in PD. Although incompletely understood, neuroinflammation influenced by microglia may be a significant contributing factor in PD etiology.

A significant role of microglia in the pathogenesis of PD is also evident in PD-linked mutations. As mentioned earlier, there are well-defined genetic mutations, SNCA, LRRK2, PRKN, DJ-1, UCHL1, and PINK1, which are involved in PD. The SNCA gene encodes α-synuclein, and missense mutations and multiplications of this gene lead to the development of PD (Ibanez et al. 2009; Singleton et al. 2003). These mutations can activate microglia (Kam et al. 2020) because of the complex interplay between microglia and α-synuclein (Choi et al. 2020; Ferreira and Romero-Ramos 2018; Wang et al. 2015). Activated microglia are predominantly involved in the clearance of excess α-synuclein in the cytoplasm, α-synuclein also activates microglia, causing neuronal toxicity by production of ROS (Jin et al. 2007; Zhang et al. 2005). Furthermore, α-synuclein reduces microglial phagocytosis, leading to impaired clearance of aggregated proteins or cellular debris (Choi et al. 2015). A recent study showed that knockdown of LRRK2 inhibited microglial proinflammatory responses in cell culture model (Daher et al. 2014). SN neurons were also found to be protected in LRRK2 knockout mice following lipopolysaccharides (LPS) induced neuroinflammation as well as adeno-associated virus-mediated transduction of human α-synuclein. Interestingly, these studies also showed that under normal conditions, the LRRK2 expression was undetectable in the mid-brain of wild-type mice. However, its expression is increased in inducible nitric oxide synthase (iNOS)-positive myeloid cells in the SN neurons following overexpression of α-synuclein or exposure to LPS. These findings support the role of LRRK2 in the clearance of α-synuclein and activation of microglia. Similarly, the effect of PRKN mutation on microglia was detected in PARKIN−/−murine glial culture (Solano et al. 2008). It supported the microglial population more than the astrocytes when compared with wild-type cultures. Another cell culture study with PINK1 mutation demonstrated reduced proinflammatory and antiinflammatory cytokine production in microglia following LPS/interferon-gamma (IFN-γ) stimulation. These findings in animal models with genetic mutations and in cell culture studies strongly indicate that microglia play a critical role in the pathogenesis of PD.

Astroglia

Along with microglia, astrocytes also contribute to neurodegenerative diseases (Teismann and Schulz 2004). Glial fibrillary acidic protein (GFAP), an astrocytic marker was isolated from demyelinated multiple sclerosis (MS) plaques (Eng et al. 2000). Astrocytes are the most abundant glial cell types in the brain (Miller 2018). Based on their location and morphological features, protoplasmic and fibrous astrocytes are located in the grey and white matter, respectively (Miller 2018). The highly ramified protoplasmic astrocytes maintain integrity of the blood-brain barrier (BBB) (Alvarez et al. 2013; Cabezas et al. 2014; Heithoff et al. 2021; Obermeier et al. 2013). An increased level of proinflammatory cytokines changes BBB permeability (Wong et al. 2004). The communication changes between astrocytes and blood vessels induce astrocytes to become reactive (Alvarez et al. 2013). Moreover, studies have localized the aggregation of α-synuclein only in protoplasmic astrocytes, making these astrocytes relevant to the onset and progression of PD (Braak et al. 2006; Halliday and Stevens 2011). Astrocytes are also a critical source of specific factors required for neuronal differentiation and survival (Allen and Eroglu 2017; Barreto et al. 2011; Christopherson et al. 2005; Chung et al. 2015; Dringen 2000; Molofsky et al. 2014). Glial cell-line derived neurotrophic factor (GDNF) secreted by astrocytes promotes survival of SN neurons (Sariola and Saarma 2003; Yasuda and Mochizuki 2010). Indeed, the maintenance of SN neurons is a crucial function of astrocytes, since a decreased level of GDNF may lead to SN neuronal death and ultimately Parkinsonian symptoms (Betarbet et al. 2000). These critical functions of astrocytes indicate they could be actively involved in the pathogenesis of PD. Notably, a subpopulation of astrocytes in basal ganglia plays circuit-specific roles and could possibly regulate the striatal function (Martin et al. 2015). Further studies of this sub-population of astrocytes may provide insights into the vulnerability of basal ganglia and the resulting development of neurodegenerative diseases.

Recent genomic and transcriptomic studies suggest that astrocytes function in a highly context-dependent manner. Moreover, there are different astrocytic subpopulations, which can either support the ongoing disease process or suppress it (Bayraktar et al. 2020; Liddelow and Barres 2017; Liddelow et al. 2017; Molofsky et al. 2014; Wheeler and Quintana 2019); Lin et al. 2017; Rothhammer et al. 2016; Wheeler et al. 2020). Like microglia, two astrocyte phenotypes have been detected in the brain (Fig. 1), A1 and A2, and they are associated with neuroinflammation and ischemia, respectively (Liddelow et al. 2017). Liddelow et al. (2017) suggested that A1 astrocytes may be harmful, because they up-regulate classical complement cascade genes which damage synapses. In contrast, A2 astrocytes up-regulate many neurotrophic factors, which support neuronal growth and survival in the developing and mature brain. This study showed that activated microglia secrete proinflammatory cytokines interleukin 1 α (IL-1 α), tumor necrosis factor (TNF), and complement component 1, subcomponent q (C1q). These factors promoted A1 phenotypical astrocytes in the CNS after injury (Fig. 1). Other intrinsic and extrinsic factors also determine the fate of astrocytes following CNS insult. Some of these factors are age and sex dependent (Johnson et al. 2008). Both astrocytes and microglia are shown to release different cytokines and other inflammatory mediators during CNS inflammation (Shields et al. 2020; Tang and Le 2016; Tay et al. 2017; Yang and Zhou 2019). As depicted in Fig. 1, reactive astrocytes detected in neurodegenerative diseases are induced by activated microglia

following LPS exposiue. Crosstalk between these glial cells appears to modulate inflammation (Liddelow et al. 2017). Moreover, ongoing molecular events due to oxidative stress, autophagy, or inflammation may influence each other in the neurodegenerative process (Fig. 2a–c). The genetic alterations associated with PD are also expressed in astrocytes, strongly suggesting that glial participation is crucial in the pathogenesis of the disease.

T cells

The CNS is understood to possess immune privilege. Microglia, the innate immune cells of the brain provide immune surveillance and maintenance. Unlike microglia, adaptive immune cells, such as T cells, can participate in both the inflammation and recovery processes in CNS diseases (Luckheeram et al. 2012). Activated T cells can infiltrate the brain and promote neurodegeneration as found in animal models of PD (Kustrimovic et al. 2016). In general, T cells are classified based on their use of CD4 and CD8 co-receptors to bind to major histocompatibility complex (MHC) molecules. CD8 + cytotoxic T cells interact with MHC class I molecules, whereas CD4 + helper T cells interact with and recognize the antigen presented by MHC class II molecules (Huang et al. 2009). These CD4 + T cells are further phenotypically differentiated into specific subtypes: Th1, Th2, Th17, and regulatory T cells (Tregs). Cytokine signaling pathways regulate this differentiation and activate lineage-specific transcription factors and epigenetic modifications (Chabot et al. 2001; Codarri et al. 2011). These CD4 + T cells in the CNS are observed in neurological disorders, especially in autoimmune diseases like MS (Codarri et al. 2011; Komuczki et al. 2019). CD4 + T cells are also detected in human CNS and animal models of PD (Brochard et al. 2009; Haque et al. 2020; Samantaray et al. 2015), AD (Baruch et al. 2015; Dansokho et al. 2016; Monsonego et al. 2003), and stroke (Ito et al. 2019). Their presence in neurological disorders suggests that CD4 + T cells are involved in neuroinflammation. Recent studies have shown that activation of calcium activated neutral protease (calpain) and CD4 + T cells are linked with the pathology of MS, PD, traumatic brain injury (TBI), spinal cord injury (SCI), and optic nerve crush injury, while calpain inhibition attenuates inflammatory T cells and promotes the recovery process (Haque et al. 2020; Hauben and Schwartz 2003; Kipnis et al. 2003; Moalem et al. 1999; Samantaray et al. 2015). Contrary to this, the inflammatory CD4 + T cell population present in ischemia-reperfusion injury and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) treated mice are harmful to neurons (Brochard et al. 2009; Haque et al. 2020; Hum et al. 2007; Samantaray et al. 2015). Based on evidence in different injury models, the role of T cell sub-populations can be either detrimental or supportive at the injury site, suggesting that the presence of local cues plays a significant role in directing T cell functions (Filiano et al. 2017).

The widely-used PD animal model, 6-hydroxydopamine (6OHDA), shows an increase in microglial MHC II expression (Cicchetti et al. 2002; Fuzzati-Armentero et al. 2019), which may activate CD4 + T cells. A study by Brochard et al. (2009) demonstrated the presence of CD8 + as well as CD4 + T cells in the SN of post-mortem PD patients and mice treated with MPTP. Additionally, CD4 + T cells (not CD8 + T cells) are detrimental to SN neurons in mice treated with MPTP (Brochard et al. 2009). This study showed that CD4 + T cell toxicity was dependent on the Fas/FasL pathway rather than the IFN-γ pathway. Studies

performed in our laboratory also observed a distinct subpopulation of CD4 + T cells in animal models of PD (Haque et al. 2020; Samantaray et al. 2015) following MPTP injection. Interestingly, further characterization of CD4 + T cells suggested that the inflammatory CD4 + T cells are granzyme B/perforin expressing cells in MPTP mice, while the regulatory T cell (Tregs) population decreased following MPTP injection. Moreover, the calpain inhibitor calpeptin modulated the activation of granzyme B and perforin producing splenic T cell populations after MPTP treatment, significantly inhibiting this distinct sub-population of CD4 + T cells. Treatment of MPTP mice with calpeptin restored the Treg population. Along with these changes, calpain inhibition protected SN dopaminergic neurons from degeneration (Haque et al. 2020). The mechanisms and pathways related to this CD4 + T cell function in MPTP mice are still under investigation, but suppression of inflammation by calpeptin may reduce the damage to SN neurons following MPTP treatment. Our findings (Haque et al. 2020; Podbielska et al. 2016; Samantaray et al. 2015) suggest that calpain activates microglia, astroglia, and T cells following MPTP treatment. However, calpeptin prevents calpain activation and neuroinflammation with resulting SN dopaminergic neuronal survival (Haque et al. 2020; Samantaray et al. 2015). Thus, calpain may have pathogenic potential in both neuronal cell death and immune cell activation.

Kustrimovic and collaborators (Kustrimovic et al. 2016, 2018) evaluated PD patient blood samples to evaluate the role of peripheral adaptive immunity in PD. They found CD4 + T cells expresses dopaminergic receptors (Kustrimovic et al. 2014), and immature CD4 + T cells from PD patients mostly differentiate into the Th1 lineage, a proinflammatory phenotype (Kustrimovic et al. 2018). CD4 + T cells also produced an increased amount of IFN-γ and TNF-α in PD patients, suggesting the peripheral immune system plays an important role in the disease process.

Oxidative stress

Mitochondria

Aging is one of the leading factors associated with PD and AD. Studies have demonstrated the manifestation of oxidative stress in CNS cells due to ongoing cellular activity (Fig. 2c), supporting a crucial role of the mitochondria in oxidative damage, as seen in PD (Andersen 2004; Blesa et al. 2015; Dias et al. 2013; Guo et al. 2018; Maguire-Zeiss et al. 2005). Any dysfunction of this cell organelle can be detrimental to cell function and viability. SN neurons in PD patients demonstrate specific complex I deficits (Schapira et al. 1990b) associated with mitochondrial dysfunction (Schapira et al. 1990a). MPTP and rotenone are commonly used toxins to create an animal model for PD. These toxins target complex I and damage mid-brain SN dopaminergic neurons (Betarbet et al. 2000; Hoglinger et al. 2005; Martinez and Greenamyre 2012; Testa et al. 2005) and motor neurons in the spinal cord (Samantaray et al. 2007). The extensive arborization of single nigrostriatal dopaminergic neurons (Matsuda et al. 2009) increases the susceptibility of the mitochondria to oxidative damage, due to the high energy demands of these neurons (Ge et al. 2020). Oxidative damage to mitochondria plays a crucial role in the onset and/or progression of PD. Additionally, the pathogenic form of α-synuclein inhibits complex I, causing mitochondrial degeneration (Martin et al. 2006). These studies also indicate that environmental toxins may

be a significant contributing factor in sporadic PD (Betarbet et al. 2000; Johnson et al. 2019; Klingelhoefer and Reichmann 2015).

Mutations detected in PD confirm the active participation of mitochondria in PD pathogenesis (Gautier et al. 2008; Ge et al. 2020; Kumar et al. 2020; Marongiu et al. 2009; Mouton-Liger et al. 2017). PINK1 and Parkin are required to maintain mitochondrial integrity (Guo 2012); these proteins also regulate mitophagy (Deas et al. 2011; Jin and Youle 2012). ROS-induced mitochondrial dysfunction is one of the factors associated with aging (Cui et al. 2012), suggesting that mitochondrial functional impairment is detrimental for dopaminergic SN cells; however, SN neuronal loss due to mitochondrial dysfunction is not observed in all PD cases.

Reactive Oxygen Species (ROS)

Oxidative stress occurs due to the imbalance between production of ROS and the availability of antioxidants or radical scavengers (Forrester et al. 2018; Ng et al. 2013; Pizzino et al. 2017) Oxidative stress is an important factor in cell death in response to a variety of pathophysiological conditions (Fig. 2c). Different pathways generate ROS in the brain during routine cellular processes; however, sometimes either overproduction or defective clearance leads to the accumulation of these free radicals (Dias et al. 2013). Mitochondria are significant contributors to ROS production (Cui et al. 2012), but oxidative stress is also reported to result from defective lipid peroxidation (Niki 2008), DNA damage (Narciso et al. 2016), formation of insoluble Parkin aggregates, decreased E3 ligase activity (LaVoie et al. 2007), and possibly α-synuclein aggregation (Scudamore and Ciossek 2018). Dopamine metabolism also results in ROS production, probably contributing to SN dopaminergic neuron vulnerability to oxidative damage (Jenner 2003). Dopamine undergoes auto-oxidation and produces dopamine quinones along with free radicals. Monoamine oxidase (MAO) and catechol O-methyl transferase (COMT) enzymes also participate in dopamine oxidation. MAO-B, which metabolizes dopamine in the cytosol, is localized on the astrocytic outer mitochondrial membrane. Since dopaminergic neurons utilize dopamine, the dopamine quinone formation may lead to dysfunction and ultimately death of these neurons (Burbulla et al. 2017; Miyazaki and Asanuma 2009). Post-mortem analysis of brain samples from PD patients also suggests oxidative stress in SN dopaminergic neurons (Jenner 1998; Siddiqui et al. 2012). However, oxidative stress may not be the causative factor, rather induced or activated by another pathway (Jenner 1998). The prominent participation of MAO-B in PD pathogenesis is supported by increased levels of this enzyme in PD patients (Siddiqui et al. 2012), and the MAO-B inhibitor, Seleginin, is used for treatment in these patients. Calpain inhibition also reduces ROS generation and caspase – 3 activity in cultured primary rat neurons (Podbielska et al. 2016), suggesting calpain may also promote ROS production and ultimately SN neuronal death in PD. Recent studies in our laboratory observed oxidative stress and calpain activation in MPTP mice; these effects were attenuated by calpeptin, suggesting calpain inhibition is neuroprotective for SN neurons (Haque et al. 2020; Samantaray et al. 2015).

Autophagy

Autophagy is a highly conserved cellular process in which aggregate-prone proteins are targeted for cellular degradation (Fig. 2b). Autophagy dysfunction has been associated with a variety of pathologies including neurodegenerative diseases (Anglade et al. 1997; Arotcarena et al. 2019; Cerri and Blandini 2019; Glick et al. 2010; Janda et al. 2012; Lynch-Day et al. 2012; Menzies et al. 2017). The three primary types of autophagy include: (i) Macroautophagy - the primary pathway for removal of damaged cell organelles or unused proteins; (ii) Microautophagy- lysosomes directly engulf the cytoplasm by invagination, and (iii) Chaperon-mediated autophagy (CMA)- a very selective, complex pathway (Sala et al. 2016). Macroautophagy is further divided into bulk and selective modalities. Selective autophagy removes cell organelles with specific designations, e.g., mitophagy (mitochondria removal), chlorophagy (chloroplast removal); lipophagy (lipid removal), or ribophagy (ribosome removal). PINK1 and Parkin are involved in the maintenance of mitochondrial function and cytoarchitecture (Gautier et al. 2008; Palacino et al. 2004). Gautier and collaborators (Gautier et al. 2008) observed that in PINK$^{-/-}$ mice, the loss of mitochondrial function is specific to dopaminergic circuitry, an interesting regional specificity of PINK1 related to mitochondria function. Mitophagy as a selective form of autophagy degrades mitochondria (Fig. 2b), which is regulated by PINK1 and Parkin proteins (Deas et al. 2011; Jin and Youle 2012; Marongiu et al. 2009). In familial PD, Parkin and PINK1 mutations are the most common causes of autosomal recessive parkinsonism and possibly occur in early onset of the disease (Brooks et al. 2009). The known critical role of PINK1 and Parkin in PD highlights the significance of autophagy in the disease process. Additionally, the other known mutations involved in familial PD, including SNCA, LRRK2, UCHL1, and DJ-1, are known to alter activity of the CMA pathway (Sala et al. 2016). Since CMA also plays a role in α-synuclein clearance, the altered activity of CMA has been postulated to promote aggregation of α-synuclein in PD pathogenesis (Marongiu et al. 2009; Sala et al. 2016). In addition to functional and morphological maintenance of the mitochondrial network (Gautier et al. 2008; Palacino et al. 2004), PINK1 and Parkin also critically regulate the removal of dysfunctional mitochondria through mitophagy (Deas et al. 2011).

Anglade and collaborators (Anglade et al. 1997) observed that cell death in SN dopaminergic neurons in PD patients is due to apoptosis and autophagy (Anglade et al. 1997). The detection of more than one pathway in cell death indicates molecular heterogeneity among the SN dopaminergic neurons. Studies in PD animal models have reported dysfunction of the autophagy pathway (Lynch-Day et al. 2012). Moreover, intracellular and extracellular stress can initiate the autophagy pathway (He and Klionsky 2009), suggesting that oxidative stress due to ROS formation in PD may induce autophagy and lead to degeneration of SN neurons (Janda et al. 2012). As mentioned earlier, the neuropathological hallmark of PD is the presence of aggregated α-synuclein inclusions in the cytoplasm. The pathological accumulation of this misfolded α-synuclein in PD patients may indicate a dysfunctional protein degradation process (Arotcarena et al. 2019). Since autophagy is the only known pathway in mammalian systems to degrade damaged cellular organelles and misfolded or aggregated proteins (Glick et al. 2010), its interruption might be a critical factor in accumulation of α-synuclein protein and later onset/progression of PD.

Conclusions

Multiple regionally specific cellular and molecular pathways play active roles during the Parkinsonian disease process. Moreover, these pathways interact and influence each other under normal and pathological situations. Activated microglia and astrocytes can initiate neuroinflammation and assist in the progression of pathological damage to SN neurons. Similarly, oxidative stress may be caused by various insults, like environmental toxins or age-associated mitochondrial dysfunction, leading to ROS production. In dopaminergic neurons, auto-oxidation of dopamine is a significant source of ROS that leads to neuronal oxidative stress. The high energy demands of dopaminergic neurons during the aging process may contribute to mitochondrial dysfunction and oxidative damage. Since mitophagy clears dysfunctional mitochondria from SN neurons, mutation-related impairments in autophagy of defective proteins can allow for toxic protein accumulation in the cell. The effects of aging on these molecular pathways and cellular functions are imprecisely understood; thus, future studies of these molecular pathways and their interaction with each other during normal and pathological states are critical to developing disease-specific treatments.

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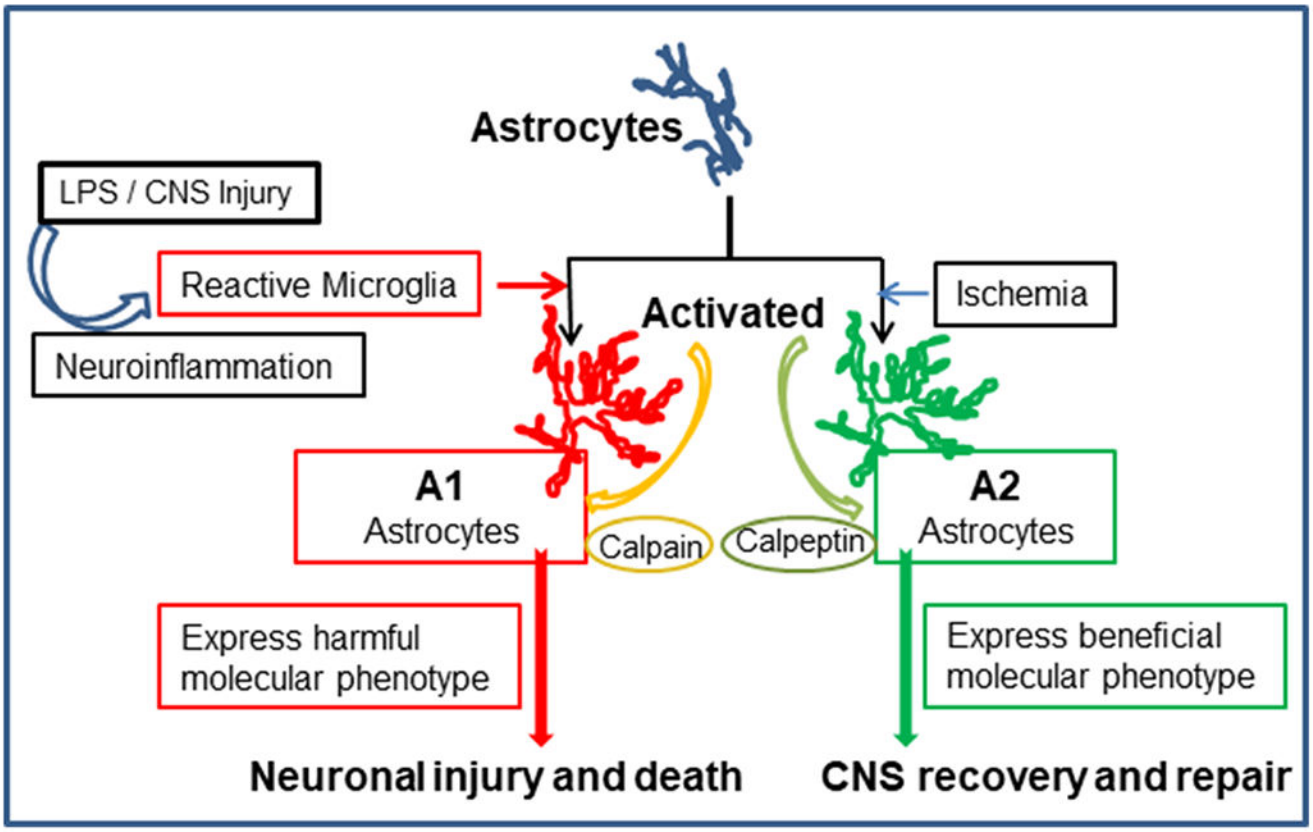

Fig. 1.

Schematic representation of astrocyte activation and differentiation following CNS injury by different types of stimuli. Microglia (triggered by different stimuli) contribute to activation of astrocytes. Depending on the micro-environment, astrocytic phenotypic differentiation may result in A1 astrocytes, which contribute to inflammation and neuronal death. However, A2 astrocytes can promote neuronal survival and recovery of function. Calpain activity may facilitate A1 astrocyte differentiation and resulting neuronal injury. However, calpain inhibition by calpeptin may contribute to neuronal survival, CNS recovery and repair through A2 astrocytic activity

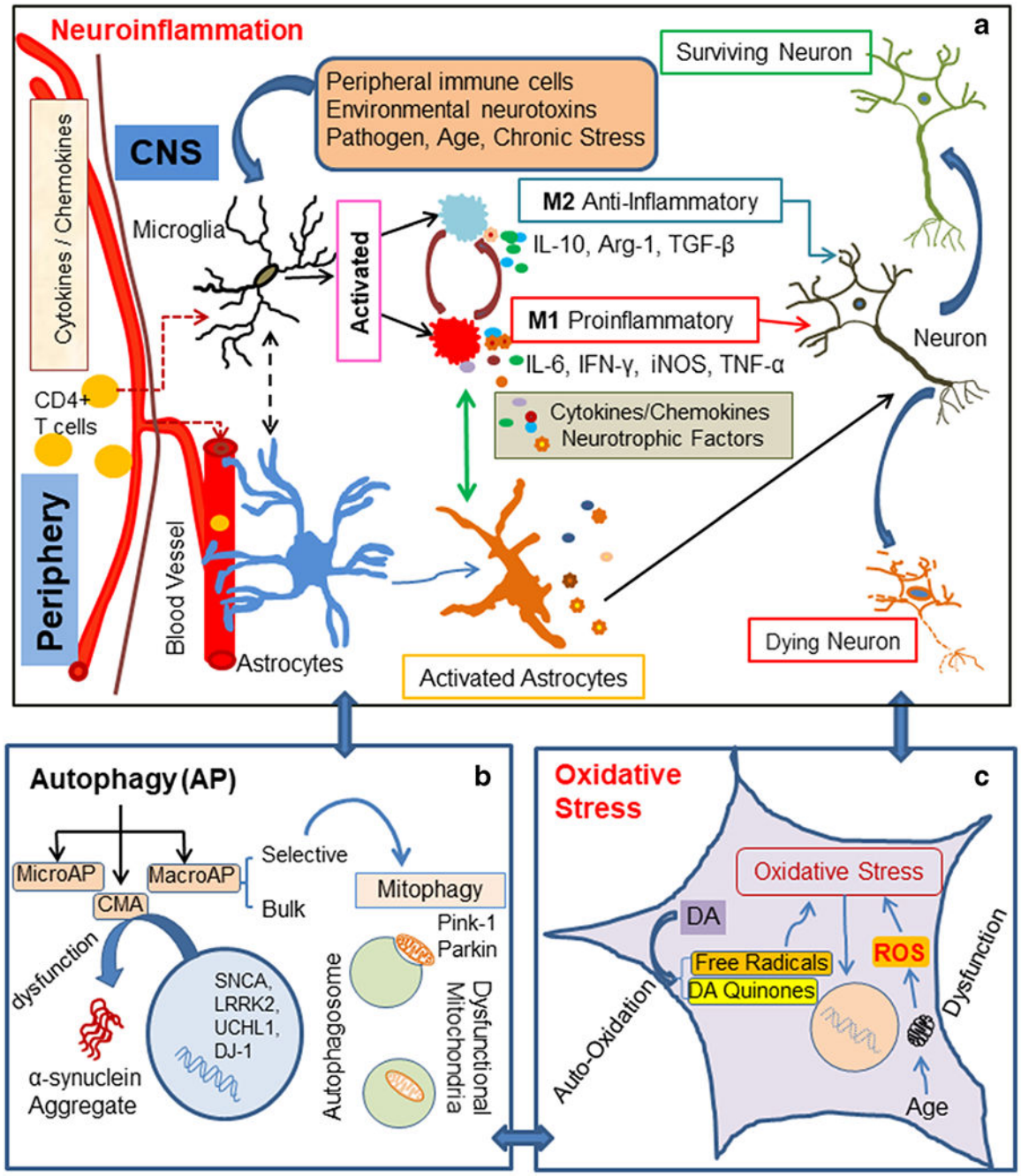

Fig. 2.

The diagram depicts several pathways involved in PD pathophysiology, **a** **Neuroinflammation** – Microglia are resident immune cells activated by various stimuli, e.g., environmental neurotoxins, pathogens, peripheral inflammation (CD4 + T cells), age, and chronic stress. These stimuli may promote divergent microglial phenotypes such as M1, a proinflammatory phenotype, which can be toxic to neurons. M1-type microglia secrete proinflammatory cytokines such as IL-1β, IL-6, IFN-γ, TNF-α, complement proteins, inducible nitric oxide synthase (iNOS), and reactive oxygen species (ROS). M2, an

antiinflammatory phenotype microglia, is believed to be neuroprotective. They secrete cytokines and growth factors such as IL-10, TGF-β, brain-derived neurotrophic factor (BDNF), and arginase-1 (Arg-1). Crosstalk between microglia and astrocytes may promote a time dependent secretion of cytokines/growth factors, contributing to PD pathological conditions, **b Autophagy** - Neuroinflammation influences all three types of autophagy: (i) macroautophagy (MacroAP), (ii) microautophagy (MicroAP), and (iii) chaperon mediated autophagy (CMA). Genetic mutations may contribute to dysfunction of CMA, leading to α-synuclein aggregation. Mitophagy, a selective autophagy process, can clear dysfunctional mitochondria. Pink1 and Parkin maintain mitochondrial cytoarchitecture and function; they also regulate mitophagy. **c Oxidative stress** - Autooxidation of dopamine (DA) in dopaminergic neurons generates free radicals and DA quinone. These free radicals lead to oxidative stress. Associated with aging and specific toxins, mitochondrial dysfunction causes the generation of ROS, which ultimately results in oxidative cellular damage