Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Immunology

Mitochondrial antigen presentation: a mechanism linking Parkinson's disease to autoimmunity

Ahmed M Fahmy[1,2], Jonathan Boulais[3], Michel Desjardins[1] and Diana Matheoud[4]

Parkinson's disease (PD) is caused by the progressive loss of dopaminergic neurons and afflicts millions of people world-wide. The current treatments address only the late motor symptoms, with no cure or preventive therapeutic approaches. The contribution of dysfunctional immune mechanisms in PD has been clearly established, with an emphasis on neuroinflammation and microglial cell activation. Recent studies have widened the involvement of the immune system in this disease by clearly showing the engagement of adaptive immunity and antigen presentation processes, directly regulated by PD-related proteins, raising the question whether PD is an autoimmune disease. The contribution of autoimmune mechanisms in PD opens novel avenues for the development of preventive therapeutic approaches.

Addresses
[1] Département de Pathologie et Biologie Cellulaire, Université de Montréal, Montréal, QC H3C 3J7, Canada
[2] Molecular Medicine Research Group, Department of Reproductive Medicine, Division of Medical Research, National Research Centre (NRC), Dokki, Egypt
[3] Institut de Recherches Cliniques de Montréal, IRCM, Montréal, QC, H2W 1R7, Canada
[4] Département de Neurosciences, Université de Montréal, CRCHUM, 900 rue Saint-Denis, Montréal, H2X 0A9, Canada

Corresponding author:
Matheoud, Diana (diana.matheoud@umontreal.ca)

Current Opinion in Immunology 2019, **58**:31–37

This review comes from a themed issue on **Antigen processing**

Edited by **Justine D Mintern** and **Jose A Villadangos**

For a complete overview see the Issue and the Editorial

Available online 21th March 2019

https://doi.org/10.1016/j.coi.2019.02.004

Introduction

In the early 19th century, James Parkinson published the first description of patients presenting tremor and a loss of muscular power observed in the streets of London. This disease, which was to become known as Parkinson's disease (PD), was then further characterized by Charcot in France a few decades later who contributed the first classification of the pathology (for a recent review on the history of PD see Ref. [1]). PD is characterized by motor deficits, due to a specific loss of dopaminergic neurons (DN) in the pars compacta of the substantia nigra in the midbrain. DN control voluntary movements, thus their degeneration leads to resting tremor, muscular rigidity, bradykinesia, and postural imbalance. The primary causes of DN loss in the context of PD are still unclear. Two events provided key insights into the potential causes of the disease. A series of observations that unfold as a 'detective story' led to the identification of a simple chemical compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) as a causative agent of the disease [2]. In 1982, William Langston examined a patient sent to the emergency of the Santa Clara Valley Medical Center in San-Jose, California, who presented, literally overnight, the hallmark symptoms of PD. Within a short period of time, additional patients displaying the same condition were reported in nearby hospitals. Remarkably, these patients showed a transient reversal of their condition almost instantly after L-DOPA treatment. After a cleaver investigation, it turned out that all of these people were heroin addicts who had been exposed to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) present as a contaminant in the synthetic heroin they used. This observation indicated for the first time that environmental elements act as a trigger of the disease. Since then, MPTP is used to induce DN cell death in animal models of PD. Today, the risk associated with exposure to a wide array of environmental toxins such as pesticides, solvents, and metals is well established [3].

A second key hint that turned out to be crucial for the understanding of the disease came with the first reports linking PD to genetic mutations. In the 1990s, the field of PD was divided regarding the possible contribution of a genetic cause to the disease. The advent of positional cloning led to the discovery that a large cohort of patients, the 'Contursi kindred' [4] from a family spanning multiple generations with apparent dominant inheritance of PD, displayed the same mutation, an alanine to threonine substitution at position 53 (A53T), in the gene coding for the protein α-synuclein [5]. While little was known about the protein then, α-synuclein is now implicated in mechanisms inducing neuronal cell death by the formation of protein aggregation (Lewy bodies) [6]. So far, at least 19 genes and 23 loci have been linked to PD [7]. Although a unifying model integrating all PD-related proteins is lacking, the identification of genes and loci of susceptibility provides unique insights to

understand the molecular mechanisms involved in the etiology of the disease. Undoubtedly, the involvement of such a high number of proteins in PD would take place through complex cell biology mechanisms.

Mitochondrial antigen presentation (MitAP): a new pathway involved in PD

Mutations in two of the PD-related proteins, PINK1 and Parkin, cause an early onset form of the disease with a penetrance close to 100%, highlighting the interest to study their function to understand the molecular mechanisms associated with the development of the disease [8]. PINK1 is a mitochondrial serine/threonine-protein kinase that stabilizes the E3 ligase Parkin to depolarized mitochondria, a process that participates in the initiation of mitophagy, the process by which the cell degrades damaged mitochondria by autophagy, and the clearance of non-functional mitochondria [9,10]. A loss of function of these proteins is thus believed to lead to the accumulation of damaged mitochondria in the cytoplasm causing cell death. However, the involvement of PINK1 and Parkin through mitophagy in the development of PD *in vivo* has been difficult to validate. Indeed, knock-out mice for each of these proteins are generally healthy, without any noticeable motor impairment [11,12]. Whether this is related to the finding that both PINK1-independent and Parkin-independent pathways of mitophagy exist [13–15] remains to be determined. Remarkably, knock-in mice expressing the PD-related mutation S65A of Parkin display motor impairment without any defect in mitophagy [16]. The recent advent of new approaches to monitor mitophagy should provide further insights into the role of this process in the repression and/or activation of pathophysiological pathways contributing to the disease [17]. In the meantime, these data suggest that PINK1 and Parkin are likely to be involved in PD through other pathways.

We have shown in primary macrophages and dendritic cells, as well as in the RAW macrophage cell line, that both of these proteins repress mitochondrial antigen presentation on MHC class I molecules, a process referred to as MitAP [18]. The presentation on MHC II was not studied. In the absence of PINK1, cell treatment with the bacterial toxin lipopolysaccharide (LPS) or a short heat stress (HS) mimicking fever triggers a strong MitAP response. This process occurs independently of mitophagy, as shown by the fact that CCCP treatment, a strong inducer of mitophagy, does not stimulate MitAP. Instead, the presentation of mitochondrial antigens is driven by the formation of mitochondria-derived vesicles (MDVs). These structures were originally showed to carry oxidized cargos and fuse with lysosomes and peroxisomes [19,20]. We also observed that the treatment of cells with CCCP after HS, strongly abrogated MitAP (unpublished data), supporting the concept that mitophagy acts as a protective mechanism restricting MitAP, highlighting the possibility that these two pathways are actually connected. A protective role for mitophagy has also been proposed for the regulation of inflammation through the inhibition of the inflammasome pathway [21], supporting the notion that mitophagy acts as an immune regulator. In antigen presenting cells (APCs), MDV formation in response to LPS and HS occurs within 60 min and requires the recruitment of at least two cytoplasmic proteins to mitochondria, sorting nexin 9 (Snx9) and Rab9, both involved in vesicle formation elsewhere in the cell. MDVs then fuse with late endosomes/lysosomes, as evidenced by their accumulation in the cytoplasm in cells lacking Rab7 [18]. Thus, the time frame of MDV formation in LPS-treated cells suggests that this process is a rapid response to stress triggered as part of an initial innate immune response. Coupled with the delivery of mitochondrial content to late endosomes/lysosomes, MDV formation further engages an adaptive immune response through the processing of mitochondrial proteins for antigen presentation. Although very likely, the contribution of the MitAP pathway to presentation on MHC class II molecules remains to be established. These findings provide the first direct evidence that PD-related proteins actively regulate immune processes, highlighting the contribution of the immune system in the etiology of PD. Considering the fact that PINK1 and Parkin mutations account for only a small proportion of all PD cases, it will be interesting to determine whether other PD-related proteins modulates the MitAP pathway, including those associated with the more widely spread familial forms (e.g. the G2019S LRRK2 mutation) and sporadic PD.

Insights from PD-related proteins: the lysosome is a cornerstone of PD

In a cell biology and immunological point of view, it is striking to note that several of the PD-related proteins identified so far are associated with mitochondria and lysosomes [22,23], highlighting the potential significance of the MitAP pathway in PD. The roles of PD-related proteins in lysosomes has been reviewed recently [24]. In brief, a common feature by which mutations in these proteins might contribute to the MitAP pathway is their ability to alter lysosome function and activity. For instance, the G2019S mutation in the LRRK2 gene, which codes for a multifunctional protein partially localized to lysosomes [25], enhances the kinase activity of this protein causing the clustering of morphologically distorted lysosomes in primary fibroblasts derived from PD patients [26]. This mutation, prevalent in both familial and sporadic PD [7], also negatively regulates the maturation of phagosomes and their fusion with lysosomes [27,28]. Indeed, the finding that LRRK2 phosphorylates several Rab GTPases suggests a role for this protein as a regulator of vesicular trafficking [29]. Interestingly, the expression of LRRK2 is increased in immune cells from PD patients, suggesting its involvement in immune mechanisms [30]. Another PD-related protein with a link to lysosomes is α-synuclein. Aggregation of this protein impairs lysosomal function through perturbation of

hydrolase trafficking [31]. Mazzulli *et al.* have shown that α-synuclein aggregation in human induced-pluripotent-stem-cell-derived neurons from Gaucher disease patients alters lysosome function and results in neurotoxicity [32]. Gaucher disease is caused by mutations in the glucocerebrosidase (GBA) gene, coding for a lysosomal enzyme involved in lipid metabolism, which are also a common risk factor for PD [33]. Mutations in other PD-related proteins also affect lysosomal properties. A PD-associated mutation in VPS35 (D620N),which normally function in endosomal cargo recognition, alters the distribution of endosomes and the trafficking of Cathepsin D, a protease that degrades α-synuclein, in PD patients [34–36]. A decrease in the level of cathepsin D was also observed in nigral neurons from PD patients compared with age-matched controls [37]. Finally, the depletion of ATP13A2, a P-type ATPase with mutations associated to an early onset form of PD [38], decreases the expression of SYT11, another PD-related protein, which impairs lysosomal function and autophagic degradation [39]. The lower expression of SYT11 also increases the pH of lysosomes and decreases the activity of cathepsin L [39], an endopeptidase involved in antigen processing [40]. These data suggest that alterations in multiple PD-related proteins decrease lysosomal activity. Although counter-intuitive, a decrease in lysosomal activity favors the generation of peptides for T cell stimulation by preventing the premature and complete degradation of proteins [41]. The effect of the modification of lysosomal properties associated with the dysfunction of PD-related proteins on antigen presentation has not been directly addressed so far. However, it can be argued that a loss of lysosomal function would favor antigen presentation and mechanisms related to MitAP.

Is PD an autoimmune disease?

Several evidence supports the contribution of autoimmunity in PD. Autoantibodies against antigens from proteins relevant to PD, such as α-synuclein [42], as well as CD4+ and CD8+ T cells specific for autoantigens against this protein have been identified in PD patients [43]. In contrast, regulatory T cell suppressive functions are altered in PD patients [44], while adoptive transfer of regulatory T cells in a MPTP murine model of PD effectively protects the animals against neurodegeneration [45]. Genome-wide association studies (GWAS) have revealed the association of immune loci, such as HLA [46] with PD, reinforcing the idea of a possible implication of the adaptive immune response in the disease. Analysis of GWAS data also found an association between PD and several autoimmune diseases, including type 1 diabetes, Crohn disease, ulcerative colitis, rheumatoid arthritis, celiac disease, psoriasis, and multiple sclerosis [47].

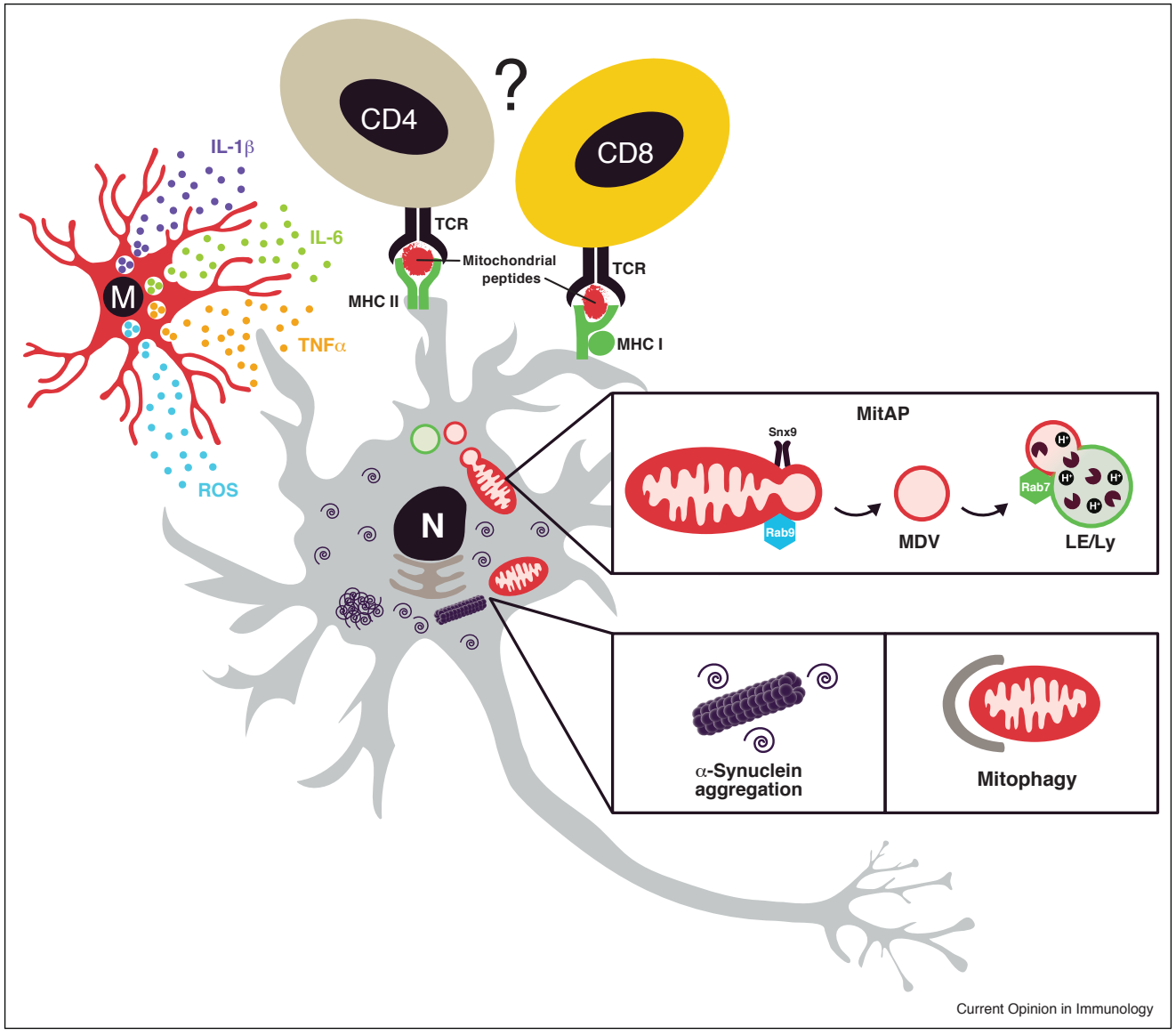
An increase in the presentation of mitochondrial antigens in the absence of PINK1 or Parkin is also likely to trigger an autoimmune response. Indeed, because the immune system is able to recognize and mount an efficient response against bacteria phylogenetically related to mitochondria, it might be beneficial to limit the exposure of mitochondrial antigens to the immune system [48]. For example, primary biliary cholangitis (PBC) is a liver autoimmune disease affecting predominantly woman and characterized by high titers of antimitochondrial antibodies and anti-mitochondria-specific CD4 and CD8+ T cell activities [49].

In PINK1 KO mice, MitAP is strongly induced upon intra-venous LPS treatment in APCs in the periphery, including dendritic cells isolated from the spleen [18]. Whether the TLR pathway is involved in this process has not been addressed yet. Such an eventuality raises the interesting question whether infection with Gram-negative bacteria would also activate MitAP. This is of particular interest considering the recent finding showing the involvement of the intestinal microbiome, which is significantly altered during gut infection, in the development of PD [50]. With antigen presentation in mind, it is possible to propose a model where MitAP in PINK1 and Parkin KO mice is initially triggered in the periphery in response to cell stress. MitAP activation in APCs would lead to the establishment of mitochondria-specific CD8+ T cells. The potential involvement of such T cells in the destruction of DNs would require at least two important steps. First, these cells would have to cross the blood-brain-barrier and enter into the brain. The presence of activated T cells in the blood of PD patients as well as infiltration in the brain has been observed [51–53]. In the brain, T cells would then have to recognize and attack DNs, a process that would be possible if these neurons were to present the proper mitochondrial antigens, presumably through the engagement of the MitAP pathway. Interestingly, the group of David Sulzer in New York provided a strong support for the involvement of autoimmunity in PD by showing that inflammatory conditions trigger the expression of MHC-I molecules at the surface of DNs, rendering them susceptible to CD8+ T cell attack [54]. Along this line, a recent study has shown that Th17 CD4+ T cells, a T helper cell type implicated in autoimmunity [55], are increased in the blood of newly diagnosed PD patients and can also recognize and kill iPSC-derived midbrain neurons [56]. The involvement of T cells in the destruction of DNs, that can be described as a 'Non-autonomous cell death' pathway [57], contrasts with 'Cell-autonomous' models where the loss of DNs is caused by an accumulation of toxic materials such as damaged mitochondria and aggregated α-synuclein [58] (see Figure 1).

Future perspectives

PD is generally considered to be a disease of the brain associated with the destruction of DNs. This view somehow obliterates the fact that an ensemble of non-motor prodromal symptoms linked to the disease are observed many years, often more than a decade, before the

Figure 1



Current hypothesis for the etiology of PD.
In the context of PD, DN are exposed to the activated immune system: the first line of immune defense in the brain corresponds to microglia (M). In inflammatory conditions present in PD, microglial cells secrete pro-inflammatory cytokines and produce ROS creating a neurotoxic environment. T cells (CD4 and CD8) infiltrate the brain of PD patients and are found in close contact with DN. Among infiltrating T cells, mitochondrial-specific T cells are proposed to play a role in DN cell death. Mitochondrial-specific T cells would recognize mitochondrial peptides on MHC-I and/or MHC-II molecules presented at the surface of DNs. The generation of these peptides reflects the induction of MitAP in DN (upper frame): Mitochondria-derived vesicles (MDVs) are formed after Snx9 and Rab9 recruitment to the mitochondria. MDVs then fuse with the late endosomal/lysosomal compartment (LE/Ly) in a Rab7-dependent manner, enabling the processing of mitochondrial proteins into peptides. Peptides then associate with MHC-I and/or II for presentation at the surface. Microglia and T-cell-mediated DN cell death are then non-cell-autonomous mechanisms. In contrast, cell-autonomous models have also been proposed. One hypothesis is that α-synuclein aggregation and accumulation induce DN degeneration. A second hypothesis is that mitochondria dysfunction and in particular defects in mitophagy lead to the accumulation of damaged mitochondria causing a strong oxidative stress in DN contributing to cell death.

emergence of motor impairment [59]. These may include alterations not related to the dopamine system such as a loss of the sense of smell, depressive moods and constipation. This supports the concept that determinants acting from the periphery, away from the brain, may participate in the initiation of PD. An exciting proposal highlights the existence of a gut–brain axis in the disease. It was shown, for example, that implantation of the microbiota of PD patients in an asymptomatic mouse model of PD (mice overexpressing α-synuclein) leads

to the emergence of motor impairment [50], highlighting the fact that alteration of the human microbiome is a risk factor of PD. Bacterial infection is known to affects and modifies the microbiota [60]. In that context, the observation that a bacterial component like LPS induces MitAP [18] suggests that gut infection with Gram-negative bacteria might also contribute to PD pathogenesis. A link between infectious diseases and PD has been discussed. Indeed, an increase in PD was, for example, reported after the 1918 flu pandemic [61]. It would also be interesting to determine whether environmental risk factors for PD such as exposure to pesticides could activate the MitAP pathway. Indeed, one such compound, rotenone, inhibits the mitochondrial complex I and induces a high mitochondrial stress [62].

The time line of the prodromal symptoms clearly highlights the fact that a window of opportunities exists to target the molecular mechanisms that may act as initiators of the disease. This led, for example, to the development of treatments targeting neuroinflammation, an important pathophysiological condition contributing to the development of PD. Nonsteroidal Anti-Inflammatory Drugs (NAIDs) have been associated with a lower risk to develop PD in epidemiological studies and in animal models of PD [63]. Moreover, a recent study showing that among patients with IBD, in which a higher incidence of PD is observed, early exposure to anti-inflammatory anti-TNF therapy was associated with reduced PD incidence [64]. Recently PD related genes have been implicated in the regulation of inflammation. PD related LRRK2 mutations R1441G and G2019S, were shown to mediate peripheral inflammation leading to neurodegeneration *in vivo* [65]. In addition to their role in the control of the MitAP pathway, PINK1 and Parkin have been shown to modulate the release of pro-inflammatory cytokines through the cGAS/STING pathway [66]. The implication of specific molecules and pathways regulating inflammation in PD, would allow a more targeted therapeutic approach. In a similar way, the implication of autoimmunity in PD pathobiology opens novel avenues for the development of therapeutic approaches.

Conflict of interest statement

Nothing declared.

Acknowledgements

This work was supported by the Weston Foundation, the CIHR, the NSERC and Parkinson Canada.

References

1. Goetz CG: **The history of Parkinson's disease: early clinical descriptions and neurological therapies**. *Cold Spring Harb Perspect Med* 2011, **1**:a008862.
2. Langston JW: **The MPTP story**. *J Parkinsons Dis* 2017, **7**:S11-S19.
3. Goldman SM: **Environmental toxins and Parkinson's disease**. *Annu Rev Pharmacol Toxicol* 2014, **54**:141-164.
4. Golbe LI, Di Iorio G, Sanges G, Lazzarini AM, La Sala S, Bonavita V, Duvoisin RC: **Clinical genetic analysis of Parkinson's disease in the Contursi kindred**. *Ann Neurol* 1996, **40**:767-775.
5. Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H, Rubenstein J, Boyer R *et al.*: **Mutation in the alpha-synuclein gene identified in families with Parkinson's disease**. *Science* 1997, **276**:2045-2047.
6. Luk KC, Kehm V, Carroll J, Zhang B, O'Brien P, Trojanowski JQ, Lee VM: **Pathological alpha-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice**. *Science* 2012, **338**:949-953.
7. Deng H, Wang P, Jankovic J: **The genetics of Parkinson disease**. *Ageing Res Rev* 2018, **42**:72-85.
8. Schulte C, Gasser T: **Genetic basis of Parkinson's disease: inheritance, penetrance, and expression**. *Appl Clin Genet* 2011, **4**:67-80.
9. Lazarou M, Sliter DA, Kane LA, Sarraf SA, Wang C, Burman JL, Sideris DP, Fogel AI, Youle RJ: **The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy**. *Nature* 2015, **524**:309-314.
10. Narendra D, Tanaka A, Suen DF, Youle RJ: **Parkin is recruited selectively to impaired mitochondria and promotes their autophagy**. *J Cell Biol* 2008, **183**:795-803.
11. Oliveras-Salva M, Van Rompuy AS, Heeman B, Van den Haute C, Baekelandt V: **Loss-of-function rodent models for parkin and PINK1**. *J Parkinsons Dis* 2011, **1**:229-251.
12. Perez FA, Palmiter RD: **Parkin-deficient mice are not a robust model of parkinsonism**. *Proc Natl Acad Sci U S A* 2005, **102**:2174-2179.
13. Allen GF, Toth R, James J, Ganley IG: **Loss of iron triggers PINK1/Parkin-independent mitophagy**. *EMBO Rep* 2013, **14**:1127-1135.
14. Bhujabal Z, Birgisdottir AB, Sjottem E, Brenne HB, Overvatn A, Habisov S, Kirkin V, Lamark T, Johansen T: **FKBP8 recruits LC3A to mediate Parkin-independent mitophagy**. *EMBO Rep* 2017, **18**:947-961.
15. McWilliams TG, Prescott AR, Montava-Garriga L, Ball G, Singh F, Barini E, Muqit MMK, Brooks SP, Ganley IG: **Basal mitophagy occurs independently of PINK1 in mouse tissues of high metabolic demand**. *Cell Metab* 2018, **27**:439-449 e435.
16. McWilliams TG, Barini E, Pohjolan-Pirhonen R, Brooks SP, Singh F, Burel S, Balk K, Kumar A, Montava-Garriga L, Prescott AR *et al.*: **Phosphorylation of Parkin at serine 65 is essential for its activation *in vivo***. *Open Biol* 2018, **8**.
17. Williams JA, Zhao K, Jin S, Ding WX: **New methods for monitoring mitochondrial biogenesis and mitophagy *in vitro* and *in vivo***. *Exp Biol Med (Maywood)* 2017, **242**:781-787.
18. Matheoud D, Sugiura A, Bellemare-Pelletier A, Laplante A, Rondeau C, Chemali M, Fazel A, Bergeron JJ, Trudeau LE, Burelle Y *et al.*: **Parkinson's disease-related proteins PINK1 and Parkin repress mitochondrial antigen presentation**. *Cell* 2016, **166**:314-327.
19. Neuspiel M, Schauss AC, Braschi E, Zunino R, Rippstein P, Rachubinski RA, Andrade-Navarro MA, McBride HM: **Cargo-selected transport from the mitochondria to peroxisomes is mediated by vesicular carriers**. *Curr Biol* 2008, **18**:102-108.
20. Soubannier V, McLelland GL, Zunino R, Braschi E, Rippstein P, Fon EA, McBride HM: **A vesicular transport pathway shuttles cargo from mitochondria to lysosomes**. *Curr Biol* 2012, **22**:135-141.
21. Zhong Z, Umemura A, Sanchez-Lopez E, Liang S, Shalapour S, Wong J, He F, Boassa D, Perkins G, Ali SR *et al.*: **NF-kappaB restricts inflammasome activation via elimination of damaged mitochondria**. *Cell* 2016, **164**:896-910.
22. Dehay B, Martinez-Vicente M, Caldwell GA, Caldwell KA, Yue Z, Cookson MR, Klein C, Vila M, Bezard E: **Lysosomal impairment in Parkinson's disease**. *Mov Disord* 2013, **28**:725-732.

23. Gan-Or Z, Dion PA, Rouleau GA: **Genetic perspective on the role of the autophagy-lysosome pathway in Parkinson disease**. *Autophagy* 2015, **11**:1443-1457.

24. Bourdenx M, Dehay B: **What lysosomes actually tell us about Parkinson's disease?** *Ageing Res Rev* 2016, **32**:140-149.

25. Biskup S, Moore DJ, Celsi F, Higashi S, West AB, Andrabi SA, Kurkinen K, Yu SW, Savitt JM, Waldvogel HJ *et al.*: **Localization of LRRK2 to membranous and vesicular structures in mammalian brain**. *Ann Neurol* 2006, **60**:557-569.

26. Hockey LN, Kilpatrick BS, Eden ER, Lin-Moshier Y, Brailoiu GC, Brailoiu E, Futter CE, Schapira AH, Marchant JS, Patel S: **Dysregulation of lysosomal morphology by pathogenic LRRK2 is corrected by TPC2 inhibition**. *J Cell Sci* 2015, **128**:232-238.

27. Hartlova A, Herbst S, Peltier J, Rodgers A, Bilkei-Gorzo O, Fearns A, Dill BD, Lee H, Flynn R, Cowley SA *et al.*: **LRRK2 is a negative regulator of Mycobacterium tuberculosis phagosome maturation in macrophages**. *EMBO J* 2018, **37**.

28. Kim KS, Marcogliese PC, Yang J, Callaghan SM, Resende V, Abdel-Messih E, Marras C, Visanji NP, Huang J, Schlossmacher MG *et al.*: **Regulation of myeloid cell phagocytosis by LRRK2 via WAVE2 complex stabilization is altered in Parkinson's disease**. *Proc Natl Acad Sci U S A* 2018, **115**:E5164-E5173.

29. Steger M, Tonelli F, Ito G, Davies P, Trost M, Vetter M, Wachter S, Lorentzen E, Duddy G, Wilson S *et al.*: **Phosphoproteomics reveals that Parkinson's disease kinase LRRK2 regulates a subset of Rab GTPases**. *eLife* 2016, **5**.

30. Cook DA, Kannarkat GT, Cintron AF, Butkovich LM, Fraser KB, Chang J, Grigoryan N, Factor SA, West AB, Boss JM *et al.*: **LRRK2 levels in immune cells are increased in Parkinson's disease**. *NPJ Parkinsons Dis* 2017, **3**:11.

31. Mazzulli JR, Zunke F, Isacson O, Studer L, Krainc D: **α-Synuclein-induced lysosomal dysfunction occurs through disruptions in protein trafficking in human midbrain synucleinopathy models**. *Proc Natl Acad Sci U S A* 2016, **113**:1931-1936.

32. Mazzulli JR, Xu YH, Sun Y, Knight AL, McLean PJ, Caldwell GA, Sidransky E, Grabowski GA, Krainc D: **Gaucher disease glucocerebrosidase and alpha-synuclein form a bidirectional pathogenic loop in synucleinopathies**. *Cell* 2011, **146**:37-52.

33. Sidransky E, Lopez G: **The link between the GBA gene and parkinsonism**. *Lancet Neurol* 2012, **11**:986-998.

34. Follett J, Norwood SJ, Hamilton NA, Mohan M, Kovtun O, Tay S, Zhe Y, Wood SA, Mellick GD, Silburn PA *et al.*: **The Vps35 D620N mutation linked to Parkinson's disease disrupts the cargo sorting function of retromer**. *Traffic* 2014, **15**:230-244.

35. Vilarino-Guell C, Wider C, Ross OA, Dachsel JC, Kachergus JM, Lincoln SJ, Soto-Ortolaza AI, Cobb SA, Wilhoite GJ, Bacon JA *et al.*: **VPS35 mutations in Parkinson disease**. *Am J Hum Genet* 2011, **89**:162-167.

36. Zimprich A, Benet-Pages A, Struhal W, Graf E, Eck SH, Offman MN, Haubenberger D, Spielberger S, Schulte EC, Lichtner P *et al.*: **A mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset Parkinson disease**. *Am J Hum Genet* 2011, **89**:168-175.

37. Chu Y, Dodiya H, Aebischer P, Olanow CW, Kordower JH: **Alterations in lysosomal and proteasomal markers in Parkinson's disease: relationship to alpha-synuclein inclusions**. *Neurobiol Dis* 2009, **35**:385-398.

38. Park JS, Blair NF, Sue CM: **The role of ATP13A2 in Parkinson's disease: clinical phenotypes and molecular mechanisms**. *Mov Disord* 2015, **30**:770-779.

39. Bento CF, Ashkenazi A, Jimenez-Sanchez M, Rubinsztein DC: **The Parkinson's disease-associated genes ATP13A2 and SYT11 regulate autophagy via a common pathway**. *Nat Commun* 2016, **7**:11803.

40. Hsieh CS, deRoos P, Honey K, Beers C, Rudensky AY: **A role for cathepsin L and cathepsin S in peptide generation for MHC class II presentation**. *J Immunol* 2002, **168**:2618-2625.

41. Lennon-Dumenil AM, Bakker AH, Wolf-Bryant P, Ploegh HL, Lagaudriere-Gesbert C: **A closer look at proteolysis and MHC-class-II-restricted antigen presentation**. *Curr Opin Immunol* 2002, **14**:15-21.

42. Yanamandra K, Gruden MA, Casaite V, Meskys R, Forsgren L, Morozova-Roche LA: **alpha-synuclein reactive antibodies as diagnostic biomarkers in blood sera of Parkinson's disease patients**. *PLoS One* 2011, **6**:e18513.

43. Sulzer D, Alcalay RN, Garretti F, Cote L, Kanter E, Agin-Liebes J, Liong C, McMurtrey C, Hildebrand WH, Mao X *et al.*: **T cells from patients with Parkinson's disease recognize alpha-synuclein peptides**. *Nature* 2017, **546**:656-661.

44. Saunders JA, Estes KA, Kosloski LM, Allen HE, Dempsey KM, Torres-Russotto DR, Meza JL, Santamaria PM, Bertoni JM, Murman DL *et al.*: **CD4+ regulatory and effector/memory T cell subsets profile motor dysfunction in Parkinson's disease**. *J Neuroimmune Pharmacol* 2012, **7**:927-938.

45. Reynolds AD, Banerjee R, Liu J, Gendelman HE, Mosley RL: **Neuroprotective activities of CD4+CD25+ regulatory T cells in an animal model of Parkinson's disease**. *J Leukoc Biol* 2007, **82**:1083-1094.

46. Hamza TH, Zabetian CP, Tenesa A, Laederach A, Montimurro J, Yearout D, Kay DM, Doheny KF, Paschall J, Pugh E *et al.*: **Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease**. *Nat Genet* 2010, **42**:781-785.

47. Witoelar A, Jansen IE, Wang Y, Desikan RS, Gibbs JR, Blauwendraat C, Thompson WK, Hernandez DG, Djurovic S, Schork AJ *et al.*: **Genome-wide pleiotropy between Parkinson disease and diseases**. *JAMA Neurol* 2017, **74**:780-792.

48. Baum H: **Mitochondrial antigens, molecular mimicry and autoimmune disease**. *Biochim Biophys Acta* 1995, **1271**:111-121.

49. Nishio A, Keeffe EB, Gershwin ME: **Immunopathogenesis of primary biliary cirrhosis**. *Semin Liver Dis* 2002, **22**:291-302.

50. Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, Challis C, Schretter CE, Rocha S, Gradinaru V *et al.*: **Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease**. *Cell* 2016, **167**:1469-1480 e1412.

51. Baba Y, Kuroiwa A, Uitti RJ, Wszolek ZK, Yamada T: **Alterations of T-lymphocyte populations in Parkinson disease**. *Parkinsonism Relat Disord* 2005, **11**:493-498.

52. Brochard V, Combadiere B, Prigent A, Laouar Y, Perrin A, Beray-Berthat V, Bonduelle O, Alvarez-Fischer D, Callebert J, Launay JM *et al.*: **Infiltration of CD4+ lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease**. *J Clin Invest* 2009, **119**:182-192.

53. McGeer PL, Itagaki S, Akiyama H, McGeer EG: **Rate of cell death in parkinsonism indicates active neuropathological process**. *Ann Neurol* 1988, **24**:574-576.

54. Cebrian C, Zucca FA, Mauri P, Steinbeck JA, Studer L, Scherzer CR, Kanter E, Budhu S, Mandelbaum J, Vonsattel JP *et al.*: **MHC-I expression renders catecholaminergic neurons susceptible to T-cell-mediated degeneration**. *Nat Commun* 2014, **5**:3633.

55. Bettelli E, Oukka M, Kuchroo VK: **T(H)-17 cells in the circle of immunity and autoimmunity**. *Nat Immunol* 2007, **8**:345-350.

56. Sommer A, Maxreiter F, Krach F, Fadler T, Grosch J, Maroni M, Graef D, Eberhardt E, Riemenschneider MJ, Yeo GW *et al.*: **Th17 lymphocytes induce neuronal cell death in a human iPSC-based model of Parkinson's disease**. *Cell Stem Cell* 2018, **23**:123-131 e126.

57. Dawson TM: **Non-autonomous cell death in Parkinson's disease**. *Lancet Neurol* 2008, **7**:474-475.

58. Michel PP, Hirsch EC, Hunot S: **Understanding dopaminergic cell death pathways in parkinson disease**. *Neuron* 2016, **90**:675-691.

59. Goldman JG, Postuma R: **Premotor and nonmotor features of Parkinson's disease**. *Curr Opin Neurol* 2014, **27**:434-441.

60. Lupp C, Robertson ML, Wickham ME, Sekirov I, Champion OL, Gaynor EC, Finlay BB: **Host-mediated inflammation disrupts the intestinal microbiota and promotes the overgrowth of Enterobacteriaceae**. *Cell Host Microbe* 2007, **2**:204.

61. Jang H, Boltz DA, Webster RG, Smeyne RJ: **Viral parkinsonism**. *Biochim Biophys Acta* 2009, **1792**:714-721.

62. Radad K, Rausch WD, Gille G: **Rotenone induces cell death in primary dopaminergic culture by increasing ROS production and inhibiting mitochondrial respiration**. *Neurochem Int* 2006, **49**:379-386.

63. Rocha NP, de Miranda AS, Teixeira AL: **Insights into neuroinflammation in Parkinson's disease: from biomarkers to anti-inflammatory based therapies**. *Biomed Res Int* 2015, **2015**:628192.

64. Peter I, Dubinsky M, Bressman S, Park A, Lu C, Chen N, Wang A: **Anti-tumor necrosis factor therapy and incidence of Parkinson disease among patients with inflammatory bowel disease**. *JAMA Neurol* 2018, **75**:939-946.

65. Kozina E, Sadasivan S, Jiao Y, Dou Y, Ma Z, Tan H, Kodali K, Shaw T, Peng J, Smeyne RJ: **Mutant LRRK2 mediates peripheral and central immune responses leading to neurodegeneration *in vivo***. *Brain* 2018, **141**:1753-1769.

66. Sliter DA, Martinez J, Hao L, Chen X, Sun N, Fischer TD, Burman JL, Li Y, Zhang Z, Narendra DP *et al.*: **Parkin and PINK1 mitigate STING-induced inflammation**. *Nature* 2018, **561**:258-262.