Chapter 5

Chronic Inflammation Connects the Development of Parkinson's Disease and Cancer

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Abstract

Increasing number of genetic studies suggest that the pathogenesis of Parkinson's disease (PD) and cancer may involve similar genes, pathways, and mechanisms. The differences in the pathological and cellular mechanisms, and the associated genetic mutations, may result in two such divergent diseases. However, the links between the molecular mechanisms that cause PD and cancer remain to be elucidated. This article appraises the overlapping molecular features of these diseases and discusses the implications for prevention and treatment. We propose that chronic inflammation (CI) in neurons and tumors contributes to a microenvironment that favors the amassing of DNA mutations and facilitating disease formation. CI may therefore play a key role in the development of PD and cancer, and provide a link between these two diseases.

Keywords: Parkinson's disease, cancer, chronic inflammation, neurodegenerative disease, genetic mutation

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, after Alzheimer's disease [1]. Typical symptoms include static tremors, muscle rigidity, and bradykinesia. These are caused by the premature death of dopaminergic neurons in the midbrain. The motor symptoms can be treated with dopaminergic drugs; however, the effectiveness diminishes as the severity of the clinical symptoms increases due to the development of the primary neuro-degeneration [2]. In contrast, cancer is a type of selectively advantageous cells with clonal proliferation. Although the two may appear distinctive, early epidemiological surveys have shown a connection between them. In 1954, Doshay [3] reported that the cancer

incidence rate was lower among PD patients, but the reason for this was undistinguishable. Later, several epidemiological studies of cancer showed that the incidence of cancer was generally low among PD patients, regardless of whether they smoke or not [4]. However, the incidence of thyroid cancer, breast cancer, and melanoma was relatively high [5]. A recent study covering 219,194 people with PD displayed that the rate ratio (RR) for all subsequent primary malignant cancers combined was 0.92 [95% confidence interval (CI): 0.91–0.93], including increased RRs ($p < 0.05$) of breast cancer and melanoma cancer, and decreased RRs of 11 cancers [6]. This has been the most commanding epidemiological evidence for a connection between PD and cancer. Surely, there is a difference between association and causality, and it has been proposed that the association between PD and skin cancer could be linked to the way of therapy, such as Levodopa treatment, rather than with the disease itself. However, some observations did not support the causality [7, 8]. Moreover, some people thought that the low incidence of cancer in PD patients comes from the negative relationship between PD and smoking [4]. This may widely explain the decrease of smoking-related cancers, but the reduction of non-smoking-related cancers cannot be resolved.

The unusual epidemiological relation between PD and cancer has drawn the attention of many investigators. The genetic assessment encouraged an additional understanding: most of these familial PD genes had been found and summarized to be associated with cancer (**Table 1**). Mutations found in *parkin* (*PARK2*), *PINK1* (*PARK6*), *DJ-1* (*PARK7*), and *LRRK2* (*PARK8*) might cause distinctive significances and consequences of PD and cancer, respectively, in different types of cells [9]. PD and cancer have been discovered to share a PI3K/AKT/mTOR pathway, which is a central mechanism of cell growth and proliferation that mainly functions through modulating protein synthesis and responding both intrinsic and environmental stress promptly [10]. Currently, more than 12 loci were found to be related to familial PD [11]. Among these, six genes have been cloned. The monogenic forms of PD display both autosomal dominant and recessive modes of inheritance, and account for 1–3% of late-onset disease and approximately 20% of young-onset disease [1, 12]. PD-related genes are involved in a series of cellular mechanisms including misfolding and degradation of proteins, mitochondrial damage, oxidative stress response, cell cycle control, and DNA repair. These all play a vital role in both PD and cancer. Understanding of the functions of these genes in cell survival and cell death might help to reveal the connection between the two diseases.

Gene	PD locus	Chromosome location	Inheritance in PD*	Expression in cancer	Proliferation in Cancer†	Cancer
α-Synuclein	*PARK1/PARK4*	4q21–q23	AD	Overexpressed (not express in normal tissue)	+	Brain tumors [74] Melanoma [75] Ovary cancer [76]
Parkin	*PARK2*	6q25.2–q27	AR	Decreased§	−	Glioblastoma [9] Colon cancer [9] Lung cancer [9]
UCHL1	*PARK5*	4p14	AD	Silenced	−	Nasopharyngeal carcinoma [77]

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Gene	PD locus	Chromosome location	Inheritance in PD*	Expression in cancer	Proliferation in Cancer†	Cancer
				(via CpG methylation)		Colorectal cancer [78]
PINK1	*PARK6*	1p35–p36	AR	Decreased§	–	Breast cancer [79]
DJ-1	*PARK7*	1p36	AR	Overexpressed	+	Non-small-cell lung cancer [80]
LRRK2	*PARK8*	12p11.2–q13.1	AD	Overexpressed	+	Papillary renal cell carcinoma [64], Thyroid cancer [64]

*AD, autosomal dominant; AR, autosomal recessive
§The telomeric end of chromosome 1p is subject to frequent deletion and rearrangement in many cancers
† +/− denotes proliferation and antipoliferation.

Table 1. Parkinson's disease involved genes identified in cancer.

If genetic defect was "the match that lights the fire" of PD and cancer, chronic inflammation (CI) might supply "the fuel that feeds the flames." Over the past decades, the insight on cytokine and chemokine network has contributed to invention of a series of cytokine/chemokine antagonists used for inflammatory diseases. The first clinic practice, tumor necrosis factor antagonists, has shown encouraging efficacy [13]. CI is considered as a driving force behind many chronic diseases including cancerization and neurodegeneration. In PD, there are many activated microglia surrounding the lost neuron, and experiments have shown that inflammatory reaction does help killing neurons [14]. Epidemiological surveys have shown that taking non-steroidal anti-inflammatory drugs (NSAIDs) can reduce the risk of PD development. CI has long been known to mediate a wide variety of illnesses, including neurodegenerative disease and malignant tumors [15]. In 1863, Rudolf Virchow noticed leucocytes in neoplastic tissues and proposed a connection between inflammation and cancer. The role for inflammation in tumorigenesis is now mostly accepted, and it has become an evident that an inflammatory microenvironment is an essential piece for most tumors [16]. Inflammatory mediators in the microenvironment of CI not only benefit cancer cells proliferation and escape from immunological surveillance but also cause a large number of random mutations [17]. Amassing research evidence supports the view that inflammatory mediators, some of that are direct mutagens, directly or indirectly downregulate DNA repair pathways and cell cycle checkpoints, consequently destabilizing cell genome and contributing to the accumulation of random genetic alterations. Thus, inflammation is considered as the seventh most important sign of cancer [18].

The cellular pathways and its associated mechanisms (**Figure 1**) that involve genes common to PD and cancer have been discussed in our previous paper [19]. In this manuscript, we further explain the environmental factors that cause PD and cancer from the perspective of CI and related genes to provide a better understanding and treatment options of these two diseases.

To emphasize the multiple pathological functions of these gene mutations, they are discussed separately.

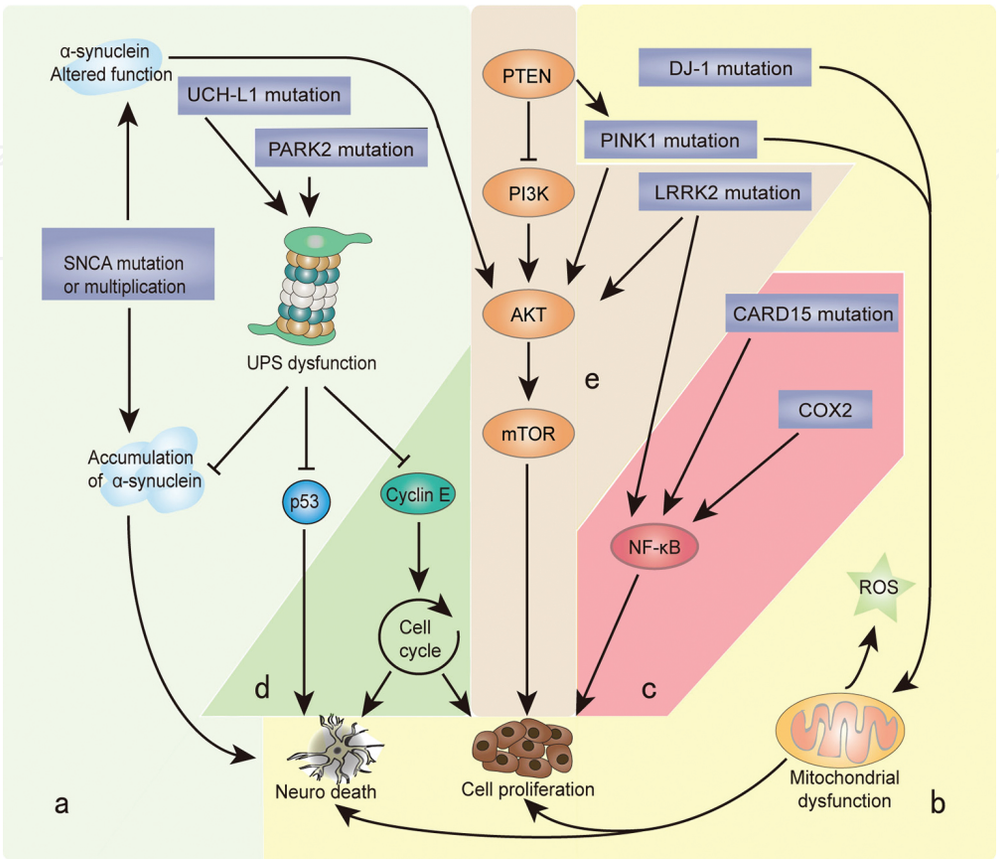

Figure 1. Overlapping genes and cellular pathways between PD and cancer.The biological connection of PD and cancer mainly includes five fields: (a) misfolding and degradation of proteins, (b) mitochondrial damage and oxidative stress response, (c) CI, (d) cell cycle control and DNA repair, and (e) PI3K/AKT/mTOR pathway regulation. The α-synuclein polymer attributed to *SNCA* multiplication is the main component of LBs. *SNCA* mutations alter the normal function of α-synuclein, which activates the PI3K/AKT/mTOR pathway and promotes cell proliferation. Under the cascade of phosphorylating AKT, PINK1, and LRRK2 can also activate mTOR. *PARK2* and *UCH-L1* mutations disrupt the degradation function of ubiquitin proteasome system (UPS) for the misfolded and aggregated α-synuclein, cyclin E, and p53. *PINK1* and *DJ-1* mutations result in the overproduction of ROS and oxidative stress in mitochondria, damaging neurons, and stimulating cell proliferation. *COX2* and *CARD15* mutations activate the NF-kB pathway and induce CI, leading to genetic mutations and oxidative stress. The different cellular backgrounds of cancer cells and neurons (mitotic vs. post-mitotic cells) bring completely distinct reactions to external stimuli and internal changes: some undergo cell proliferation and others neuron death. The final results are two serious diseases: cancer and Parkinson's disease.

2. Chronic inflammation

The blood–brain barrier (BBB) prevents the lymphatic infiltration and neurotoxins diffusion from the blood to the CNS. Conventionally, the CNS was regarded as the immunological restriction due to its limited inflammatory reaction and lymphatic infiltration. Nonetheless,

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accumulating evidence indicates that the CNS actually is the immunological specialization by the resident innate immune cell in the brain: microglia. Activated microglia could prevent the CNS injury from pathogenic factors (physiological disrupt and toxic insult) through releasing a number of cytokines and chemokines [20]. These inflammatory mediators could trigger or modulate the remove of neurotoxins and inhibit their detrimental effects. Thus, acute inflammatory responses are consider to be beneficial, but long-term, high-level CI can severely damage the body. Two of the pathological characteristics of PD are loss of dopaminergic neurons and accumulation of LBs in the nigrostriata of the midbrain. LBs are abnormal intracytoplasmic filamentous aggregates of α-synuclein present, respectively, in neurons and axons. Recent studies have shown that neurons able to release α-synuclein oligomers, which can bind to toll-like receptors (TLR) to activate microglia, activating the nuclear factor kappa B (NF-kB) pathway, and releasing of inflammatory factors. These immune factors not only act directly on dopaminergic neurons to cause neuronal death but also aggravate the inflammatory reaction and continue to activate microglia. Activated microglia surround dead neurons in the substantia nigra pars compacta (SNc) of PD patients. Studies have shown that inhibition of microglia cascade reactions can prevent degradation of neurons [21]. Increasing studies demonstrated that there was a positive correlation between SNc cell loss and microglia activation in both animal models and PD patients. Timing analysis displayed that reduce microglial activation can rescue SNc neurons loss in animal models, suggesting an active effect of microglia in killing SNc cell following a range of stimuli. It is increasingly clear that activation of microglia is a highly localized inflammatory reaction rather than generalized. Even though the degenerating neuronal terminals of SNc cell cannot stimulate the similar response but only the dopaminergic neurons in the SNc [22]. Therefore, cell death of PD directly relates to a substantial increase of microglia activation. At the same time, overproduction of free radicals (superoxide and peroxynitrite) damages the balance of the redox potential of neurons and acts on biomacromolecules to modulate their roles, or causes lipid peroxidation leading to cell death eventually. Alternatively, microglia might kill SNc cells by producing other noxious compounds including cytokines and proinflammatory prostaglandins. Patients with PD have selective degeneration of neurons in the SNc accompanied by microglial activation and a challenged immune system.

The presence of activated microglia in PD might reflect a scavenging role in the wake of a primary pathologic process. However, evidence for a more sinister role comes from animal models of PD. MPTP, 6-OHDA, lipopolysaccharide, rotenone, viruses, and SNc extracts all can lead to degeneration of the dopaminergic neurons and loss of striatal dopamine in primates, rodents, and other species [23]. Each of them can cause an inflammatory response that associated with the enhancement of microglia activation in the SNc. The best evidence for the significance of inflammation during neoplastic progression maybe come from study of cancer risk among long-term users of aspirin and NSAIDs. A big prospective study of hospital workers indicated that the incidence of PD in chronic users of over-the-counter NSAIDs which scavenge free oxygen radicals and inhibit cyclooxygenase (COX) activity was 46% lower than that of age-matched non-users [24]. Inhibition of COX-mediated dopaminergic neurons oxidation, as well as inhibition of microglial-derived toxic mediator production, is likely to be among the mechanisms that contribute to decreased incidence of PD in chronic NSAIDs

users [25]. Therapeutically, these findings raise the possibility that early involvement with NSAIDs or similar anti-inflammatory therapy may be neuroprotective and could delay or prevent onset of PD. That anti-inflammatory medications downregulate microglial responses to a toxic insult and directly reduce neuronal loss strongly, which indicates that localized inflammation is pathogenic in the SNc rather than merely a late response to neuronal death.

3. NOD2

Crohn's disease (CD), also known as regional enteritis, is a type of inflammatory bowel disease. In 2001, three laboratories found CD associate with genetic variants. Nucleotide-binding oligomerization domain protein 2 (NOD2) also known as caspase recruitment domain protein 15 (CARD15) is a protein that in humans which is encoded by the *CARD15* gene located on human chromosome 16q12 [26–28]. Approximately 40% of CD patients in the Western countries carry at least one of these three SNPs: R702W, G908R, and L1007fsinsC, and heterozygous mutation of any of these SNPs increases CD risk 2–4 times, whereas multiple-locus heterozygous mutations or homozygous mutations may lead to a CD risk higher than 20 times. However, it has been reported that none of these three SNPs was involved in CD among Chinese (Han) [29], Korean [30], and Japanese patients [31]. NOD2, encoded by *CARD15*, is the receptor of muramyl peptides (MDP), a component of bacterial peptidoglycan. Binding of MDP and NOD2 activates NF-kB, and inflammatory reaction occurs. It has also been shown that *CARD15* mutation plays a role in innate immune system and pathogen recognition in terms of other complex polygenic diseases. In 2007, Bialecka [32] showed that the three SNPs of *CARD15* (R702W, G908R, and L1007fsinsC) were significantly correlated with PD in the Polish population. Using RFLP, our group found P268S, another SNP of *CARD15*, to be a risk factor for Chinese PD. In addition, Crane et al. [33] reported that P268S was related to susceptibility of ankylosing spondylitis. Proell et al. [34] performed sequence comparison and found that NOD2 shared a high degree of similarity with apoptotic protease activating factor 1 (Apaf-1). They simulated the homologous structure of NOD2 based on Apaf-1 structure and found that P268S was located at the connexon (ligand-binding position) before the first helix of the NOD. Replacing Pro with Ser changed the conformation of the connexon and affected its binding to the substrate.

Whether the CD's-associated *CARD15* mutations lead to a loss or gain of function of the NOD2 receptor is subject to controversy, and by which mechanisms, this change in function might increase the susceptibility to CD which is still under investigation. Patients with CD are known to have an increased risk of developing colorectal cancer [35]. *CARD15* mutations may also increase the susceptibility of developing colorectal cancer in Caucasians without CD [36, 37]. These observations suggested that immune system mechanisms were involved in the pathogenesis of cell damage in CD and also provided evidence for an ongoing active pathologic process. Inflammation can be triggered by invading microbes and also be initiated from within the organism, by diseases affecting the nervous system. There are three common outcomes of inflammation. The offending agent or process is inactivated and the injury repaired. The host loses the battle and dies or suffers irreparable tissue damage. Neither the organism nor the injurious process prevails, resulting in a prolonged battle that provides fertile

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ground for the development of chronic inflammatory conditions. The last outcome may relate closely to neurodegenerative diseases and cancer, two of the greatest public health problems of this century [38].

4. COX2

COX is the central enzyme in prostaglandin biosynthesis. There are two different isoforms of COX: COX-1 and COX-2. Constitutive expression of COX-1 is commonly found in many tissues. Because COX-1 is responsible for the biosynthesis of prostaglandins which regulate some physiological homeostasis, including modulation of renal blood flow and preservation of the gastric mucosa. Normally, COX-2 could not be discovered in most tissues except for stimulating by some mitogenic and inflammatory mediators [39]. COX2 is not only key to the synthesis of prostaglandin in inflammatory reactions but also an important contributor to the degradation of neurons in PD. Inhibiting COX2 activity in mice and rats can alleviate neuronal death caused by MPTP [40] and 6-ODHA [41], respectively. Macrophages, neurons, and glial cells in the central nervous system can all express COX2. Unlike COX1, which is constitutively expressed, COX2 expression is induced by inflammatory conditions. The COX2 level in the dopaminergic neurons of PD patients is elevated, and prostanoid and ROS produced by COX2 can directly act on dopaminergic neurons causing cell toxicity [42]. The role of COX2 in inflammation and neuronal degradation has yet to be verified. However, it has been shown that NSAIDs nonselectively inhibit the activities of COX1 and COX2, thus reducing prostaglandin production and promoting clearance of ROS. An epidemiological survey has revealed that individuals who take NSAIDs have a lower risk of PD than those who do not [25]. However, there has not been any report on the effects of specific COX2 inhibitors on the occurrence and development of PD.

COX-2, the inducible isoform of prostaglandin H synthase, has been implicated in the growth and progression of a variety of human cancers [43]. There are many evidence support that COX-2 is involved in the development of cancer. Because the overexpression of COX-2 is commonly found in the premalignant and malignant tissues. The most powerful findings from genetic studies support the view that it exists a cause-and-effect relationship between COX-2 and tumorigenesis. Multiple lines of evidence indicate that COX-2 is a *bona fide* pharmacological target for anticancer therapy. Epidemiologic studies have shown a 40–50% reduction in mortality from colorectal cancer in individuals who take NSAIDs on a regular basis compared with those not taking these agents [44]. COX-2, an inducible enzyme with expression regulated by NF-kB, mediates tumorigenesis. COX2 can activate not only the NF-kB pathway, but also p38 and Jnk in the MAPK pathway [45]. High levels of COX2 have been found in many cancers, particularly colon cancer [46]. COX-2 is also expressed in 93% of melanomas, with a moderate-to-strong expression in 68% [47]. COX2 can decrease the level of arachidonic acid and inhibit cell apoptosis. It can also increase prostaglandin production and promote cell growth and differentiation. These phenomena were also observed in the clinical effect of selective COX2 inhibitors in the market [48, 49].

5. LRRK2

Leucine-rich-repeat kinase 2 (*LRRK2*) is a large gene, 144 kb in length, containing 51 exons and encoding a multi-domain kinase composed of 2527 amino acids. LRRK2 is expressed in many organs and tissues, including the brain. In 2004, two laboratories reported that *LRRK2* mutations were related to PD [50, 51]. More than 40 *LRRK2* mutations, almost all missense, have been found [52]. However, the nosogeneses of many mutations remain unclear. *LRRK2* mutations account for 10% of familial PD and 3.6% of sporadic PD, suggesting strong modifiers of *LRRK2* disease [53]. LRRK2 is a large protein (280KDs). It can activate AKT, an upstream element of the mTOR pathway, thus decreasing the anti-apoptosis activity mediated by AKT and promoting neuronal death [54]. Gene structure studies showed that LRRK2 protein was consist of five conserved domains, including a leucine-rich repeat (LRR) domain, a Roc GTPase domain, a C terminal of Roc (COR) domain, a MAPKKK mixed-lineage protein kinase domain, and a WD40 domain [55, 56]. LRRK2 contains multiple sets of internal repeats, each of which is predicted to adopt a distinct structure. Such repeats, which occur in 14% of all prokaryotic and eukaryotic proteins, commonly serve as platforms for protein interactions [57]. *LRRK2* gene was discovered as part of an evolutionarily conserved family of proteins marked by GTPase (Guanosine triphosphatase) domains usually encoded together with kinase domains [55]. The G2019S mutation in the *LRRK2* is the single most common autosomal dominantly inherited PD gene defect. The LRRK2 protein is a scaffolding-type protein kinase, and G2019S is thought to lead to the disease by increasing the LRRK2 kinase activity resulting in increased phosphorylation of as yet mostly hypothetical targets, although whether all mutations in LRRK2 have the same biochemical mechanism is uncertain [58]. Missense mutations in both the kinase and GTPase domain in LRRK2 cause late-onset PD with clinical and pathological phenotypes nearly indistinguishable from idiopathic disease, possibly through the upregulation of LRRK2 kinase activity [59]. Because the clinical phenotype ensuing from LRRK2 mutations resembles idiopathic PD, LRRK2 has emerged as, perhaps, the most relevant player in PD pathogenesis identified to date [60]. One of the consistent pathological features of patients with LRRK2 mutations is α-synuclein-positive LBs pathology [61]. Besides G2019S, there are only a handful of proven pathogenic mutations in LRRK2, which is rather surprising given its large size. Multiple pathogenic mutations (I1371V, R14441C, R1441G, R1441H, Y1699C, Y1699G, G2019S, and I2020T) are located within the GTPase and the kinase domains or within the COR domain. This structural feature can be used as a target in the design of drugs that treat PD [62]. Many of the LRRK2 kinase inhibitors identified to date were discovered by using libraries of defined kinase inhibitors [63]. As with any kinase inhibitor development for human use, issues related to safety will need to be carefully evaluated. This is particularly important for a chronic disease such as PD.

More directly supporting a role of LRRK2 in cancer, chromosomal amplification of the LRRK2 locus is required for oncogenic signaling in papillary renal and thyroid carcinomas [64]. Genetic studies have implicated LRRK2 in the pathogenesis of several human diseases, including cancer and CD [65–67]. In 2011, Liu et al. [68] found that LRRK2 could suppress the activity of the transcription factor Nuclear factor of activated T-cells (NFAT). Overexpression of LRRK2 led to increased retention of NFAT in the cytosol. When *LRRK2* was knocked

out, NFAT in the cytosol was translocated to the nucleus and transcriptionally activated the expression of genes encoding cytokines and other key proteins involved in triggering inflammatory responses. It was firstly proposed that LRRK2 might play an important role in the signal pathway that induced CD. Liu and co-workers highlighted the possibility that the M2397T (replacement of methionine 2397 with threonine) polymorphism may alter the steady-state abundance of LRRK2, which is distributed in many tissues and brain regions, generally at low abundance. In addition, the structure of LRRK2 is similar to that of carcinogen B-RAF. Therefore, it can act on the MAPK pathway. G2019S, a common *LRRK2* mutation in PD, can increase the risk of non-skin cancer in Jews by three times [69]. A complex role for LRRK2 in multiple cellular processes is perhaps not surprising, because LRRK2 has multiple domains and is both an active kinase and a GTPase [70]. Binding the different LRRK2 domains and different ligands may have different functions, preventing them from connecting closely with PD, inflammation, or cancer. To understand the roles of LRRK2 in human disease, the best place to start is with examination of the genetics linked to these diseases. Various coding changes in the open reading frame of LRRK2 are linked to disease. In PD, these mutations result in functional changes in LRRK2, although no clear pattern to these changes has emerged. LRRK2 is involved in many diseases result from the distinct influence of genetic mutations. These variants not only change the potential of LRRK2 to interact with upstream regulators or downstream effector, but also can alter the biological functions of LRRK2. The discovery of more LRRK2 functions and a deeper understanding of its pleiotropism should provide the research community with more insight into the pathological functions of the same protein in different diseases. Every protein may have more than one function and may play completely different roles in different diseases. Targeted therapies with minimal side effects may be developed based on the functions of these proteins in different signal pathways.

6. Perspective and conclusion

Increasingly epidemiologic findings demonstrated the correlation between cancer and PD in recent years, but the conclusions were not completely consistent. This is because of the differences of study management. Our understanding of the control of signaling pathways is further advanced in cancer studies compared to neurodegeneration. As a result, many small molecule inhibitors have been approved as anticancer agents or are currently being tested in clinical trials. In 2010, Datamonitor Inc. (USA) estimated that there were over 1.5 million PD patients in the USA, Japan, France, Germany, Italy, Spain, and UK combined, one-third of them in the USA. With the increasing aging of world population, the incidence of PD is increasing yearly [71]. Medication is usually the first option in the treatment of PD. Levodopa is currently the most effective medication, but long-term use can reduce the effectiveness of treatment and cause complications such as motor dysfunction. Thus, discoveries in cancer research are likely to provide a solid base upon which scientists will study the pathophysiology of neurodegenerative diseases, especially PD.

The origins of the association and interplay between cancer and PD are still a matter of debate, but increasing epigenetic modifications such as DNA acetylation, DNA methylation, and

miRNA scan conspire with genetic alterations in disease pathogenesis [72]. Recently, Gehrke et al. [73] found that *LRRK2* mutation in Drosophila model could have an antagonist effect on two miRNAs: let-7, a known tumor suppressor, and miR-184, a mediator of neurological development. This led to E2F1/DP over-expression, causing the cells to reenter the cell cycle. These will help us develop an understanding of these two diseases from opposing angles. Although, cancer and PD seem to have little in common, one due to enhanced resistance to cell death and the other due to premature cell death. However, the more we learn about the molecular genetics and cell biology of cancer and PD, the greater the overlap between these disorders appears. Both cancer and PD are thought to be the result of the interaction of genetic and environmental factors. The difference is that different reactions occur based on different cellular backgrounds: cell division and cell death. The inflammation hypothesis is considered one explanation for PD and cancer. The immune factor and ROS released from chronic inflammatory reactions not only promote the occurrence of the disease but also cause cellular DNA to accumulate mutations more easily, forming proteins with aberrant functions. In the end, interactions between genes and the environment cause the diseases. Recently, our group found that P268S in *CARD15* may be a risk factor for PD, and Liu and co-workers provide evidence that *LRRK2* also has a role in a signaling pathway linked with the pathogenesis of Crohn's disease, an inflammatory bowel disease. These findings both implied a correlation between PD and inflammation.

Most degenerative diseases of the brain are incurable and the study of tissue from the brains of people with significant neurodegeneration is difficult, so the postmortem specimen is probably the most valuable research material. However, academic and clinic of cancer research have accumulated a wide range of achievement in the past long time, and these results and experience must be important and beneficial to neurodegeneration study. Understanding the nature of their relationship must help scientist find novel and more efficacious therapeutic approaches for both diseases.

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