Review

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Unravelling the genetic links between Parkinson's disease and lung cancer

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Abstract: Increase evidence from epidemiological studies have shown an inverse association between Parkinson's disease (PD) and lung cancer. PD and lung cancer are both geriatric diseases, where these two diseases are sharing some common genetic determinants. Several PD-associated genes including alpha synuclein (SNCA), PTEN-induced kinase 1 (PINK1), parkin, parkinsonism associated deglycase (DJ-1), leucine-rich repeat kinase 2 (LRRK2), F-box protein 7 (FBXO7) and ubiquitin C-terminal hydrolase L1 (UCHL1) were reported to have altered expressions in lung cancer patients. This indicates that certain PD-associated genes might be important in conferring anticancer effects. This review aims to depict the physiological functions of these genes, and discuss the putative roles of these PD-associated genes in lung cancer. The understanding of the roles of these genes in the lung cancer progression might be important in the identification of new treatment targets for lung cancer. Gene therapy that aims to alter the expressions of these genes could be developed for future anticancer therapy. As a result, studying the roles of these genes in lung cancer may also help to understand their involvements as well as their roles in the pathogenesis of PD.

Keywords: lung cancer; non-small cell lung carcinoma; Parkinson's disease; PD-associated genes; small cell lung cancer; targeted therapy.

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Introduction

In the past 30 years, accumulating evidence have reported a negative association between Parkinson's disease (PD) and lung cancer (Becker et al. 2010; Freedman et al. 2016; Park et al. 2019a). In the latest meta-analysis conducted by our group, the diagnosis of PD was associated with a 44% reduced risk of lung cancer (Leong et al. 2021). PD is the second most common neurodegenerative disease that is affecting 1% of the population above 60 years (Tysnes and Storstein 2017). The pathological hallmark of this disease is the loss of dopaminergic neurons in the substantia nigra (Jankovic 2008). PD is characterized by deteriorated motor features including tremors, muscular rigidity, postural imbalance and bradykinesia and a range of non-motor symptoms such as autonomic, cognitive and behavioral dysfunctions (Kalia and Lang 2015; Postuma et al. 2015). Etiology of PD is unknown but age is known to be the major risk factor for PD. Evidence shows that multiple cellular events such as misfolded proteins aggregations, oxidative stress, neuroinflammation, genetic mutations and protein clearance interruption are in place to trigger the neurodegeneration in PD (Maiti et al. 2017). Studies showed that 5–10% of both autosomal and inherited forms of PD are linked to genetic factors (Klein and Westenberger 2012; Maiti et al. 2017). The most common causative genes of PD include SNCA, parkin, DJ-1, PINK1, UCHL1 and LRRK2 (Deng et al. 2018; Klein and Westenberger 2012; Maiti et al. 2017; Selvaraj and Piramanayagam 2019).

Other than that, lung cancer is a highly invasive and rapidly metastasizing cancer. It is known to be one of the leading causes of death attributed to cancer worldwide. Lung cancer accounted for 18.4% of the total cancer deaths in 2018, with an estimation of 1.8 million deaths worldwide (Bray et al. 2018). It is the leading cause of mortality in patients aged between 40 and 80 years old (Howlader et al. 2014). Although lung cancer treatments have been improved in the past decades, lung cancer prognosis is still poor, and the 5 year survival rate remains low (Allemani et al. 2018). Lung cancer is classified into two broad categories, which are non-small cell lung carcinoma (NSCLC) and small cell

lung cancer (SCLC) (Testa et al. 2018). 15 percent of lung cancers are represented by SCLC, an aggressively malignant tumor exhibiting neuroendocrine characteristics. SCLC is found to be strongly associated with smoking (Furrukh 2013). On the other hand, 85% of lung cancer cases are represented by NSCLC and it can be further categorized into adenocarcinoma (40%), squamous cell carcinoma (20–30%) and large cell carcinoma (5–10%) (Zappa and Mousa 2016). Most of the NSCLC patients are diagnosed at an advanced stage with median overall survival ranges between 7 and 12 months, depending on the histology types and therapeutic strategies (Schad et al. 2018). Lung adenocarcinoma usually arises in the glandular epithelium of lung parenchyma consisting of type II pneumocytes whereas lung squamous cell carcinoma originates from the basal cells in the central airways (Pikor et al. 2013; Travis et al. 2011). In contrast, large cell carcinoma is an undifferentiated tumor harboring neuroendocrine features (Pikor et al. 2013).

Previously, lung cancer and PD are two diseases thought to be unrelated to each other. However, recent emerging evidence suggests that they not only share some common risk factors such as aging, but also share some common genetic features. For instance, some PD-associated genes were also reported in the pathology of lung cancer (Lebovitz et al. 2021; Liu et al. 2015). A study by Liu et al. identified elevated expressions of these PD-associated genes in NSCLC patients where the tumor samples were collected at the time of surgical resection (Liu et al. 2015). Therefore, this review aims to depict the physiological functions of PD-associated genes, followed by in-depth discussions on the putative roles of these genes in lung cancer with a focus on the molecular connections between lung cancer and PD (Table 1).

Table 1: PD-associated genes and their putative roles identified in lung cancer.

Gene	Gene locus	Expression in lung cancer	Putative roles in lung cancer
SNCA	Chromosome 4q21.2–q22 (Kim et al. 2014; Oczkowska et al. 2013)	Downregulation	EGFR trafficking Bcl-2 regulated apoptosis[a]
Parkin	Chromosome 6q25–q27 (Cesari et al. 2003; Quinn et al. 2020)	Upregulation	Cell cycle progression (cyclin E ubiquitination) (Park et al. 2019b; Veeriah et al. 2010) EGFR trafficking and PI3K-Akt pathway regulation (Eps 15 ubiquitination) (Fallon et al. 2006; Husnjak and Dikic 2006) Mitophagy (PHB2 regulation)
PINK1	Chromosome 1p36.12 (Quinn et al. 2020)	Upregulation	Cell migration and proliferation (mitophagy) (Lu et al. 2020) Cell survival and proliferation (NF-κB pathway regulation) (Zhang et al. 2017) Bcl-2 regulated apoptosis (Liu et al. 2018)
DJ-1	Chromosome 1p36.23 (Zhang et al. 2020b)	Upregulation	PI3k-Akt pathway regulation (antagonist of PTEN) (Kim et al. 2005a; Yang et al. 2005) p53-mediated apoptosis (Shinbo et al. 2005; Vasseur et al. 2009)
FBXO7	Chromosome 22q12–q13 (Conedera et al. 2016)	Upregulation	Cell cycle progression and cell proliferation (cyclin D-CDK6 formation) (Laman 2006; Laman et al. 2005) Cell cycle progression (NF-κB pathway regulation *via* cIAP1) (Chang et al. 2006; Kuiken et al. 2012)
UCHL1	Chromosome 4p14 (Ragland et al. 2009)	Upregulation	Cell proliferation (deubiquitination of cyclins)[a] (MAPK and PI3K-Akt pathways activation) (Hurst-Kennedy et al. 2012; Kim et al. 2009)

Current therapeutic strategies for lung cancer and their drawbacks

The current therapies for lung cancer include surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy or combined modality approach. Surgery is the standard of care for early-stage lung cancer patients (Dómine et al. 2020; Raman et al. 2018). Radiotherapy is another option for the early-stage patients, which damages DNA within cancerous cells (Zappa and Mousa 2016). For advanced-stage patients, a regimen of platinum-based chemotherapy (cisplatin or carboplatin) in combination

Table 1: (continued)

Gene	Gene locus	Expression in lung cancer	Putative roles in lung cancer
LRRK2	Chromosome 12p11.2–q13.1 (Zimprich et al. 2004)	Downregulation	ERK and JNK dependent autophagy (Herzig et al. 2011; Tian et al. 2021)

Elevated expressions of parkin, PINK1, DJ-1, FBXO7 and UCHL1 and downregulation of SNCA and LRRK2 were detected in lung cancer. These genes regulate cell proliferation, cell survival, apoptosis, mitophagy/autophagy and cell cycle progression *via* various signaling pathways in order to promote lung carcinogenesis. Abbreviations: SNCA, alpha synuclein; PINK1, PTEN-induced putative kinase one; FBXO7, F-box protein 7; UCHL1, ubiquitin carboxyl-terminal esterase L1; LRRK2, leucine-rich repeat kinase two; EGFR, epidermal growth factor receptor; Bcl-2, B-cell lymphoma two; PI3k-Akt, phosphatidylinositol 3-kinase-protein kinase B; Eps 15, epidermal growth factor receptor pathway substrate 15; PHB2, prohibitin two; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PTEN, phosphatase and tensin homolog; CDK6, cyclin-dependent kinase 6; CIAP1, cellular inhibitor of apoptosis one; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinases.
[a]Putative roles remain speculative.

with gemcitabine, pemetrexed, irinotecan or docetaxel is administered for a total of 4–6 cycles as first-line treatment for both NSCLC and SCLC patients (Chan and Coward 2013; Masters et al. 2015). However, the combinations of chemotherapy and radiotherapy only confer modest benefit in prolonging the overall survival as well as reducing the adverse events (Dómine et al. 2020; Zappa and Mousa 2016).

Targeted therapies involve the use of molecular inhibitors to block specific signaling pathways specifically. For instance, gefitinib, erlotinib and ceritinib which belong to the drug class of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), are the reversible competitors of ATP that bind to EGFR tyrosine kinase domain. These inhibitors are used to treat NSCLC patients with EGFR mutations with either L858R substitutions in exon 21 or amino acid deletions in exon 19 (Abidin et al. 2010; Rothschild 2014; Testa et al. 2018). Another FDA-approved agent known as crizotinib is an inhibitor of ALK, MET and ROS tyrosine kinases (Kazandjian et al. 2014; Solomon et al. 2014). These treatment strategies are promising as they confer progression-free survival longer than chemotherapy (Li et al. 2008; Richer et al. 2015; Rothschild 2014). Unfortunately, these therapies have some drawbacks, for instance, targeted therapies often result in gain-of-function mutations that lead to additional drug resistance characteristics in cancer cells. For example, the EGFR T790M mutation in exon 20, which resulted from prolonged EGFR TKI therapy, was known to disrupt the inhibitory activities of the TKIs (Kobayashi et al. 2005; Sun et al. 2013). Resistance to first-and second-generation EGFR TKIs which is caused by this mutation can be overcome by several third-generation irreversible EGFR TKIs such as osimertinib (Mok et al. 2017; Soria et al. 2018). Nevertheless, acquired resistance to osimertinib has been reported in several cases. Furthermore, a broad spectrum of drug resistance including KRAS, ALK, MET, cKIT amplification, HER1, HER2 and HER3 upregulation and L1196M mutations has been discovered in NSCLC patients (Chen et al. 2013; Doebele et al. 2012; Papadimitrakopoulou et al. 2018; Tanizaki et al. 2012). Similar drawback was observed in the SCLC patients treated with inhibitors such as gefitinib and imatinib, with no improvement in survival rate observed in small phase II trials (Abidin et al. 2010).

On top of that, immunotherapy boosts the body's natural defense systems to defeat cancer by targeting immune checkpoint pathways (Onoi et al. 2020). Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed death 1 (PD-1) and its ligand (PD-L1) are the immune checkpoint inhibitors that block the immunosuppressive mechanisms in the lung cancer cells (Kim and Choi 2020; Saltos et al. 2020). Clinical trials have revealed that immunotherapy significantly improves lung cancer patients' progression-free survival and overall survival (Kim and Choi 2020; Saltos et al. 2020). However, immune checkpoint inhibitors may cause immune-related adverse events which are resulted from non-specific activation of the immune system (Puzanov et al. 2017). This results in the high toxicities which could affect various organs including the lungs, liver, nervous system and thyroid in the patients who receiving the therapy (Kim and Choi 2020; Saltos et al. 2020).

Although there are many therapeutic agents used in the lung cancer treatment, their long-term outcomes still require further improvements. The 5 year survival rate of lung cancer patients remains low (15–20%), although it has been improved (Chen et al. 2020; Garon et al. 2019). Numerous therapeutic agents undergoing clinical trials seem to show promising results, however, the outcomes are immature and the optimal dosage and sequences are yet to be determined (Chen et al. 2020; Majeed et al. 2021). Furthermore, it is known that undesirable drug resistance and toxicity are inevitable (Chan and Hughes 2015). Disease progression has been another challenge for lung cancer therapies since lung cancer prognosis remains disappointing, with a 5 year survival rate of only approximately 15% (Edwards et al. 2014). Hence, a better understanding on the roles of these PD-associated genes and identifying the escape pathways in lung cancer could be significant in discovering new treatment strategies for lung cancer.

SNCA

SNCA encodes α-synuclein which is a 140 amino acid protein that consists of three distinct structural domains including an N-terminal region (residues 1–60), a central hydrophobic region (residues 61–95) and a C-terminal region (residues 96–140) (Kim et al. 2014; Snead and Eliezer 2014). α-Synuclein is abundantly found within the Lewy bodies, the pathological hallmark of PD, as amyloid fibrils (Kim et al. 2014; Spillantini 1999). Several variants with missense mutations (A53T, E46K and A30P, H50Q and G51D) have been identified in the cases of familial PD (Appel-Cresswell et al. 2013; Lesage et al. 2013; Proukakis et al. 2013). These mutations are believed to either accelerate the aggregation rate of fibrils formation or change the conformation or oligomerization upon aggregations (Meade et al. 2019; Snead and Eliezer 2014). Physiological functions of α-synuclein have been related to the regulation of synaptic vesicles for the release of neurotransmitters such as dopamine (Butler et al. 2017; Janezic et al. 2013) and the regulation of endoplasmic reticulum-Golgi transport (Cooper et al. 2006). Overexpression of SNCA has been reported in PD (Stefanis 2012; Tagliafierro and Chiba-Falek 2016). Aggregates of α-synuclein, especially the soluble oligomeric form, exert neurotoxicity that precedes synaptic dysfunction and ultimately cause neuronal cell death (Ingelsson 2016).

In PD, overexpression of wild-type or mutated SNCA triggered mitochondrial-mediated apoptosis that leads to neuronal cell death. This mechanism is thought to be mediated by the upregulation of Bax and downregulation of Bcl-xL as a result of interaction between SNCA and Bad, a pro-apoptotic member of the Bcl-family (Ahmad et al. 2007; Seo et al. 2002). Bad initiates allosteric activation of Bax to promote conformational change, resulting in cytochrome c release and caspases activation (Ahmad et al. 2007; Seo et al. 2002). Other than that, SNCA activates phosphatidylinositol 3-kinase-protein kinase B (PI3K-Akt) at a low expression level and subsequently increases expressions of anti-apoptotic Bcl-family members in neuronal cells. PI3K-Akt phosphorylates Akt, which activates Bad phosphorylation, thereby reducing interaction between Bad and Bcl-xL and inhibiting actions of caspase-9 (Matsuzaki et al. 1999; Pugazhenthi et al. 2000; Tsujimoto and Shimizu 2000). Through this pathway, cell death is inactivated.

Even though most research studied the actions of SNCA in brain diseases, there are evidence showing the ubiquitous presence of alpha-synuclein protein in the gastro-enteric tract and human body fluids such as blood, saliva, and cerebrospinal fluid (Campo et al. 2019; El-Agnaf et al. 2006; Fenyi et al. 2019; Gao et al. 2015). This suggests that the pro-apoptotic action of overexpressed/mutated SNCA can be observed in the peripheral organs too, including those which are prone to cancer development (Gao et al. 2015; Hansson et al. 2014; Wang et al. 2016). Additionally, animal works have shown that α-synuclein can cross the blood-brain barrier due to compromised blood-brain barrier integrity in PD (Brochard et al. 2009; Gray and Woulfe 2015; Peelaerts et al. 2015). In relation to lung cancer, a study by Yan et al. showed that SNCA is downregulated in lung adenocarcinoma (Yan et al. 2018). Bioinformatics analyses done by this group had suggested the tumor suppressive roles of SNCA (Yan et al. 2018). Hence, high expression of SNCA in lung adenocarcinoma patients would improve the overall survival time and post-progression survival time in the lung adenocarcinoma patients (Yan et al. 2018). It is possible that the reduced lung cancer risk in PD may be associated with an increased apoptosis in cancer cells (Figure 1). This could be attributed to the overexpression of SNCA in PD patients, which contributes to a better tumor suppressing ability. On the contrary, downregulation of SNCA in lung cancer patients may have promoted cancer proliferation and inhibition of apoptosis in the cancer cells (Ge and Xu 2016; West et al. 2005).

A negative association between SNCA and EGFR signaling pathway has also been reported (Yan et al. 2018) (Figure 1). EGFR plays an important role in cells proliferation, differentiation, inflammatory processes and survival (Lemmon and Schlessinger 2010; Schlessinger 2014). Upon binding to a ligand, EGFR undergoes dimerization followed by autophosphorylation that leads to activation of various downstream signaling pathways (Bethune et al. 2010; Guo et al. 2015). In NSCLC, abnormal EGFR trafficking increases cell proliferation *via* inhibition of apoptosis and thereby induces tumor development (Sigismund et al. 2018). The previous study also suggested that EGFR might suppress the SNCA expression through protein phosphorylation at four possible EGFR phosphorylation sites, which were identified from the full-length SNCA protein sequence (Yan et al. 2018). However, the mechanisms of EGFR on the SNCA regulation in lung adenocarcinoma remain elusive and require more investigations.

Parkin

Parkin gene mutation is the second most common cause of familial PD of which the majority accounts for autosomal recessive PD (Dawson and Dawson 2014; Kitada et al. 1998).

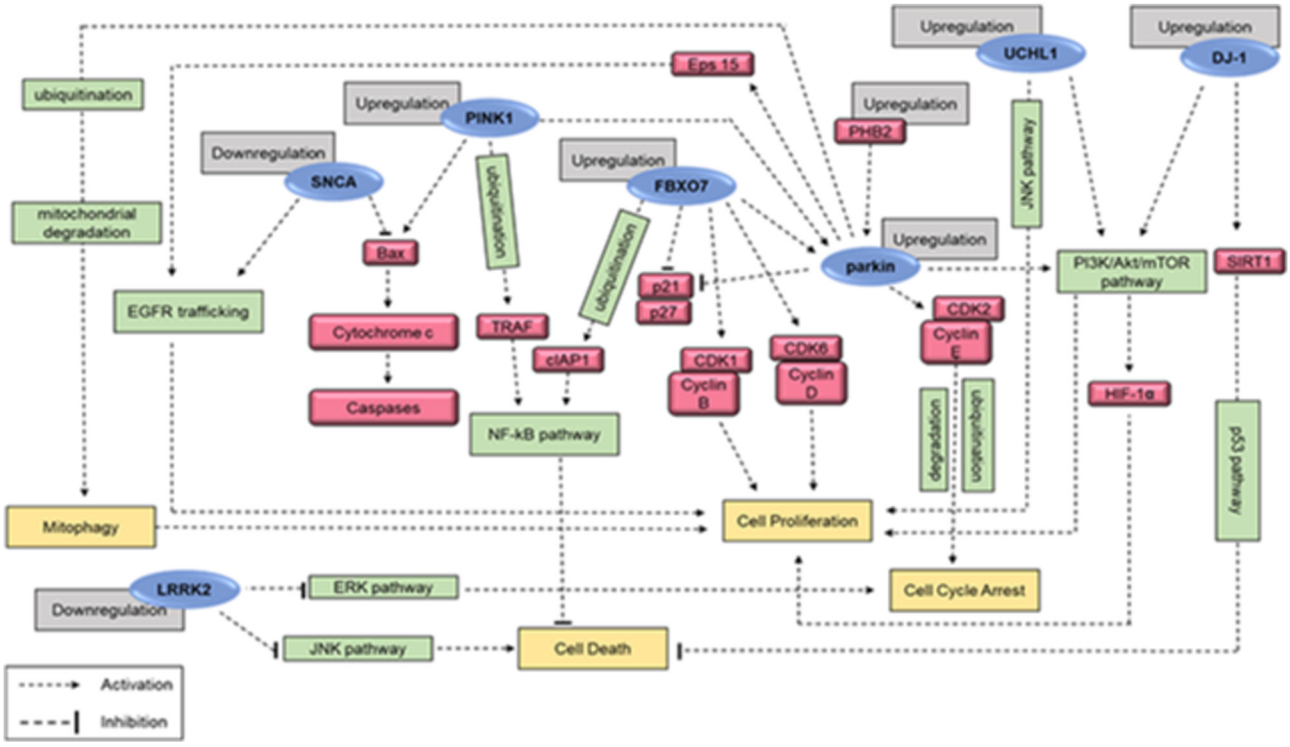

Figure 1: Lung cancer metabolism mediated by PD-associated genes. Elevated expressions of Parkin, PINK1, DJ-1, FBXO7 and UCHL1 and downregulation of SNCA and LRRK2 were detected in lung cancer. These genes regulate cell proliferation, cell survival, apoptosis, mitophagy/autophagy and cell cycle progression via various signaling pathways in order to promote lung carcinogenesis. CDK1/2/6, cyclin-dependent kinase 1/2/6; CIAP1, cellular inhibitor of apoptosis one; DJ-1, parkinsonism associated deglycase; EGFR, epidermal growth factor receptor; Eps 15, epidermal growth factor receptor pathway substrate 15; ERK, extracellular signal-regulated kinase; FBXO7, F-box protein 7; HIF-1α, hypoxia-inducible factor 1α; JNK, c-Jun N-terminal kinases; LRRK2, leucine-rich repeat kinase two; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PHB2, prohibitin two; PINK1, PTEN-induced putative kinase one; PI3k/Akt/mTOR, phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin; SNCA, alpha synuclein; SIRT1, sirtuin one; TRAF6, tumor necrosis factor receptor-associated factor 6; UCHL1, ubiquitin carboxyl-terminal esterase L1.

Parkin (also known as PARK2) functions as E3 ubiquitin ligase and comprises a ubiquitin-like domain and four zinc-coordinating RING-like domains, including RING0, RING1 IBR and RING2 (Seirafi et al. 2015). It ubiquitinates various cytosolic and outer mitochondrial membrane proteins for the coordination of cellular pathways such as mitochondrial homeostasis, anti-oxidative stress, mitophagy, protein degradation and tumor suppression (Bernardini et al. 2017; Cesari et al. 2003; Pickrell and Youle 2015; Zhang et al. 2016). Under normal circumstances, parkin mediates neuroprotection by activating the NF-κB pathway during stress. Parkin initiates ubiquitination of IKKγ and TRAF2, leading to the upregulation of pro-survival genes (Henn et al. 2007). Phosphorylation of ubiquitin and the recruitment of parkin to the damaged mitochondria by PINK1 result in mitochondrial degradation through mitophagy, which is the autophagy-lysosome pathway, as a way to maintain mitochondrial quality for cell survival (Bogetofte et al. 2019). In PD pathogenesis, parkin mutations lead to the loss of parkin function. Besides, parkin dysfunction due to oxidative stress or dopaminergic stress has been indicated in sporadic PD (LaVoie et al. 2005; Meng et al. 2011). Studies demonstrated that the nonreceptor tyrosine kinase c-Abl phosphorylates parkin, causing the inhibition of parkin's ubiquitination and the loss of its neuroprotective ability (Imam et al. 2011; Ko et al. 2010). As a result, the loss of parkin activity accumulates the number of depolarized mitochondria that produce reactive oxygen species (ROS) extensively (McWilliams and Muqit 2017; Pickrell and Youle 2015).

A growing number of studies have revealed the tumor suppressive roles of parkin in lung cancer development (Figure 1). According to a data analysis on cBio portal (Cerami et al. 2012), the frequencies of parkin mutations in lung squamous cell carcinoma and lung adenocarcinoma are about 5.6 and 3%, respectively (Xu et al. 2014). A study by Picchio et al. identified the presence of heterogenous deletions of parkin at exon 2 in lung adenocarcinoma cell lines (Cesari et al. 2003; Picchio et al. 2004). The deletions or mutations of parkin inactivate ubiquitination to cyclin E and results in the loss of its tumor suppressive effect in lung

cancer cells (Spruck et al. 1999). Cyclin E is an oncogene that is essential to cell cycle progression by regulating the transitions between cell cycle phases (Mazumder et al. 2004). Cyclin E is usually overexpressed in patients with early-stage NSCLC (Müller-Tidow et al. 2001). Notably, parkin loses its ability to ubiquitinate and degrade cyclin E by preventing the binding between cyclin E and CDK2 (Veeriah et al. 2010). This could promote cell cycle progression (Veeriah et al. 2010). Other than that, studies claim that parkin is overexpressed in both NSCLC cell lines and human NSCLC tissue samples (Duan et al. 2019; Park et al. 2019b). Overexpression of parkin in NSCLC was found to inhibit cascades of signaling pathways including cell proliferation, invasion, cell cycle progression as well as apoptosis (Duan et al. 2019). The study by Park et al. also highlighted that depletion of parkin inhibits tumorigenesis *via* cell cycle arrest at sub G0/G1 phase in NSCLC cells (Park et al. 2019b). *In vitro* ubiquitination assays showed that parkin deficiency restricts cell cycle progression by inhibiting p21 degradation and cyclin E/CDK2 complex formation (Park et al. 2019b). Moreover, depletion of parkin activates EGFR but suppresses Akt/mTOR pathways and subsequently enhances apoptosis (Duan et al. 2019; Fallon et al. 2006; Husnjak and Dikic 2006; Xiong et al. 2015). Previous study state that parkin protein mediates the monoubiquitination of Eps15, an adaptor protein found in EGFR endocytosis and trafficking (Fallon et al. 2006; Husnjak and Dikic 2006). The authors also revealed the binding of a ubiquitin-like domain in parkin to ubiquitin-interacting motifs of Eps15, which activates EGFR endocytosis and PI3K-Akt signaling pathway, a pathway that promotes cells growth and survival. A study by Zhang et al. revealed that the inner mitochondrial membrane protein called prohibitin 2 (PHB2) is highly expressed in NSCLC cells (Zhang et al. 2020a). PHB2 functions as a mitophagy receptor to the ligand autophagosomal membrane-associated protein LC3 (Wei et al. 2017). PHB2 accumulation upregulates the expressions of mitophagy-associated proteins in the tumor cells which in turn enhances the parkin-mediated mitophagy (Zhang et al. 2020a). In malignant tumors, dysregulated mitophagy is associated with metastasis of cancers and provides a survival advantage to tumor cells (Wang et al. 2020; Zhang et al. 2020a). Cancerous cells eliminate dysfunctional or damaged mitochondria *via* mitophagy and reduce ROS levels to maintain the cell survival (Humpton et al. 2019; Zhao et al. 2019).

PINK1

PTEN-induced kinase 1 (PINK1), also known as PARK6, is a serine/threonine kinase that contributes to the regulation of mitochondrial quality control pathways *via* mitophagy (Ge et al. 2020; Gonçalves and Morais 2021; Quinn et al. 2020). The loss-of-function of PINK1 is also associated with autosomal recessive and early onset of PD (Ge et al. 2020). PINK1 and parkin are mutually interdependent in mitophagy activation by which PINK1 is initiated by mitochondrial membrane potential depolarization to phosphorylate ubiquitin and parkin (Gonçalves and Morais 2021). In response to mitochondrial damage, PINK1 recruits parkin from the cytosol to depolarized mitochondria and initiates mitophagy by eliminating the damaged organelles through autophagosome recruitment and ubiquitin proteasomal degradation (McWilliams and Muqit 2017; Pickrell and Youle 2015). In PD, PINK1 mutation is associated with mitochondrial dysfunction, which triggers oxidative stress (Gautier et al. 2008; Matsuda et al. 2013). Likewise, a mutation in PINK1 can lead to failure in recruiting parkin and subsequently result in the accumulation of damaged mitochondria (Gonçalves and Morais 2021). Also, PINK1 deficiency reduces oxidative phosphorylation due to ROS accumulation and transmembrane potential dissipation (Gautier et al. 2008; Gonçalves and Morais 2021; Vara-Perez et al. 2019). This eventually causes neurodegeneration such as loss of dopaminergic neurons of the substantia nigra pars compacta.

Besides, several studies suggested that the putative roles of PINK1 in cancer development involve regulations of mitophagy, cell survival and cell cycle (Dai et al. 2019; Lu et al. 2020; O'Flanagan et al. 2015) (Figure 1). Emerging evidence have reported an upregulation of PINK1 protein expression in both NSCLC cell lines and human NSCLC tissues (Liu et al. 2018; Lu et al. 2020; Zhang et al. 2017). These studies demonstrated that PINK1 promotes cancer cell survival and proliferation which can lead to the emergence of chemoresistance in NSCLC cells *via* the NF-κB pathway (Chang et al. 2018; Zhang et al. 2017). PINK1 protein binds to tumor necrosis factor receptor-associated factor 6 (TRAF6) and facilitates ubiquitination of TRAF6 whereby it activates the NF-κB pathway (Chen et al. 2011; Zhang et al. 2017). Furthermore, a study by Dai et al. revealed increased ROS production, increased cell death, inhibited mitophagy and reduced cell proliferation in PINK1 depleted NSCLC cell lines (Dai et al. 2019). Researchers also indicated that knockdown of PINK1 enhances apoptosis of lung cancer cells *via* caspase 9 or caspase 3 activation (Dai et al. 2019; Liu et al. 2018; Zhang et al. 2017). In addition, downregulation of Bcl-2 levels and upregulation of Bax levels have been revealed in lung cancer cells (Liu et al. 2018). Bcl-2 family regulates the apoptotic pathway where Bcl-2, the anti-apoptotic proteins, and Bax, the pro-apoptotic proteins are the two key members (Liu et al. 2018). Hence, high PINK1 expression could serve as an indicator of poor prognosis in NSCLC patients (Chang et al. 2018).

DJ-1

DJ-1 is comprised of 189 amino acids and usually appears as dimers. It is expressed in almost all cells including neurons, glial cells, macrophages and cancerous cells (Ariga et al. 2013). The *PARK7* gene encodes DJ-1 and its mutations including L166P, M26I, D149A, A104T, E64D and L10P are linked to familial PD which usually result in loss of function and conformational change of protein (Bonifati et al. 2003; Moore et al. 2005). On top of that, DJ-1 is found to be overexpressed in reactive astrocytes in sporadic PD and other neurodegenerative diseases under oxidative stress (Ariga et al. 2013). DJ-1 is known to be involved in the regulation of transcription factors such as Nrf2, PI3K and p53, mitochondrial regulation, signal transduction and anti-oxidative stress reaction (Ariga et al. 2013; Kim et al. 2005b; McCoy and Cookson 2011; Zhang et al. 2020b). DJ-1 is also a sensor of oxidative stress which protects cells against free radical assault on the three cysteine residues at amino acids 46 (C46), 53 (C53) and 106 (C106) (Taira et al. 2004; Zheng et al. 2018). Of these, C106 of DJ-1 is highly susceptible to oxidative stress and is sequentially oxidized into sulfenated form (–SOH), sulfinated form ($–SO_2H$), and sulfonic form ($–SO_3H$) (Ariga et al. 2013). Oxidation of C106 to SO_3H results in inactive form of DJ-1 and lead to the loss of its biological function under extensive oxidative stress (Mita et al. 2018). As a result, excessive oxidized DJ-1 is correlated with the progression of PD due to its loss of function.

On top of that, DJ-1 is responsible for regulation of various transcription factors including nuclear factor Nrf2, PI3K/PKB, and p53 signal pathways upon oxidative stress induction. DJ-1 can either binds to p53 directly to restore the transcriptional activity or stimulate deacylation and suppress p53 transcriptional activity (Dolgacheva et al. 2019). p53 is a tumor suppressor gene that is known as 'guardian of the genome' by regulating DNA repair, cell cycle and cell death (Dolgacheva et al. 2019; Feroz and Sheikh 2020). DJ-1 protects neurons against caspase activation and cell death *via* p53-mediated Bax expression (Bretaud et al. 2007). However, p53 undergoes lysine acetylation to activate cell cycle arrest or cell death pathways and repair damaged DNA in response to damage incurred (Feroz and Sheikh 2020). Increased p53 levels and activities are associated with increased levels of cytokines, caspase 3 and Bax in the brain of the PD patients (Gandhi and Wood 2005; Mogi et al. 2007). DJ-1 can suppress p53 transcriptional activity by decreasing Bax expressions as well as stimulating post-translational modifications of p53 with acetylation and Topors-mediated sumoylation (Dolgacheva et al. 2019; Fan et al. 2008; Shinbo et al. 2005).

Aberrant protein expression of DJ-1 has been implicated in NSCLC and served as a prognostic marker that predicts poor outcomes in lung cancer patients (Kim et al. 2005a; MacKeigan et al. 2003; Zeng et al. 2011). However, the mechanism of DJ-1 in lung cancer remains ambiguous. DJ-1 overexpression is frequently found in various malignancies serving as a potent activator of the PI3K/Akt/mTOR pathway and the inhibitor of p53-mediated apoptosis (Shinbo et al. 2005; Vasseur et al. 2009) (Figure 1). DJ-1 functions as an antagonist of PTEN tumor suppressor to promote cancer cell survival by enhancing Akt phosphorylation (Kim et al. 2005a). Activation of the PI3K-Akt pathway upregulates hypoxia-inducible factor 1α (HIF-1α) expressions under hypoxic conditions leading to a series of cancer signaling events involving angiogenesis, cell proliferation and metastasis (Zhong et al. 1999).

The negative association between DJ-1 and p53 has played a role in lung carcinogenesis. Takahashi-Niki et al. revealed that DJ-1 inhibits p53 activity by activating a lysine deacetylase called SIRT1, the member of Sirtuin family protein, in A549 lung adenocarcinoma cell line (Takahashi-Niki et al. 2016). p53 mutations were detected in 34% of NSCLC patients with a higher frequency in squamous cell carcinomas than adenocarcinomas (Molina-Vila et al. 2014; Zhang et al. 2019). Genetic abnormality of p53 in lung cancers is associated with poor prognosis (Scoccianti et al. 2012; Szymanowska et al. 2005). Evidence also links p53 and Akt to the chemosensitivity against combinational cisplatin chemotherapy in NSCLC (Yilmaz et al. 2019). Cisplatin treatment or cellular stress triggers the phosphorylation of p53 at serine 15 that impairs the EGFR and Akt downstream signaling cascades in NSCLC patients (Loughery et al. 2014; Vasseur et al. 2012). Inactivation of Akt, together with p53 stimulation, contributes to the ROS production. Akt suppresses p53-mediated apoptosis during chemoresistance that activates EGFR to reduce the ROS levels (Zhang et al. 2019). These preliminary findings propose the potential of p53 re-constitution or EGFR inhibitors as the therapeutic options in sensitizing chemoresistant NSCLC cells. In short, DJ-1 is a negative regulator of p53, where the upregulation of DJ-1 promotes lung cancer progression and proliferation by activating the Akt pathway (Jin 2020).

FBXO7

F-box domain-containing protein, FBXO7/PARK15, belongs to the F-box-containing protein (FBP) family that forms ubiquitin ligase complexes with cullin-1 and SKP1. These complexes are involved in regulating proteasomal

degradation and cell cycle progression (Ho et al. 2008; Laman 2006; Zhou et al. 2015). At the N-terminus, FBXO7 protein is composed of a ubiquitin-related (UbR) domain, which recruits parkin to regulate mitochondrial quality (Burchell et al. 2013). FBXO7 mutations are genetically associated with autosomal recessive juvenile PD (Fonzo et al. 2009). A previous study has suggested that the FBXO7 protein is a stress response protein (Zhou et al. 2015). FBXO7 mutations (L34R, T22M, R481C, R378G and R498X) in PD can impair the neuroprotective function and facilitate mitochondrial proteotoxicity by stimulating the formation of parkin protein aggregations (Zhou et al. 2015). Ultimately, FBOX7 dysregulation leads to neurodegeneration *via* impairment of the ubiquitin proteasome system and inhibition of mitophagy (Zhou et al. 2016; Zhou et al. 2015). Wild-type FBXO7 protein plays a vital role in cryoprotection by facilitating mitophagy under stress. However, increased FBXO7 expression leads to aggregation of deleterious FBXO7 proteins in mitochondria which disrupts mitochondria integrity and eventually causes cell death (Zhou et al. 2016).

Emerging evidence have indicated that FBXO7 plays a role in lung tumorigenesis (Laman et al. 2005; Randle and Laman 2016; Wang et al. 2014). Elevation of FBXO7 levels was detected in both lung adenocarcinoma and squamous cell carcinoma. This triggers the cell cycle progression by facilitating the activation of D cyclins and their catalytic subunit, cyclin dependent kinase (CDK6) (Laman et al. 2005; Laman 2006) (Figure 1). Upregulation of FBXO7 is not only inducing the cyclin D-CDK6 complexes formation but also downregulating CDK inhibitors (p21 and p27) expressions (Laman 2006; Meziane et al. 2011). Increased expression of cyclin D-CDK6 complexes enhances the transition of G1 to S phase to accelerate cell proliferation. On top of that, FBXO7 proteins are involved in proteasome-mediated proteolysis of hepatoma upregulated protein (HURP) (Hsu et al. 2004). FBXO7 recruits HURP at its proline-rich domain in a CDK-1-cyclin B phosphorylation-dependent manner. In NSCLC, HURP is reported to be overexpressed in a bioinformatics analysis. The study reported a negative correlation between HURP expression level with overall survival and relapse-free survival (Wang et al. 2018). Additionally, HURP is involved in several cellular processes that induce lung tumor development including cancer proliferation, invasion and migration (Wang et al. 2018). Besides, FBXO7 is found to activate ubiquitination and degradation of cellular inhibitor of apoptosis protein 1 (cIAP1) which leads to reduced NF-κB signaling activity (Chang et al. 2006; Kuiken et al. 2012; Randle and Laman 2016) (Figure 1). As such, FBXO7 is a negative regulator of NF-κB (Randle and Laman 2016). Studies showed that a high level of cIAP1 was reported in human NSCLC tissues, which inhibits apoptosis of the lung cancer cells (Chang et al. 2006; Yang et al. 2016). Thus, high levels of both FBXO7 and cIAP1 disrupt the NF-κB pathway. NF-κB influences lung tumorigenesis by suppressing apoptosis and inducing metastasis and cell proliferation (Rasmi et al. 2020).

UCHL1

Ubiquitin C-terminal hydrolase L1 (UCHL1, also known as *PARK5*) is a ubiquitin C-terminal hydrolase that is expressed abundantly in neurons (Day and Thompson 2010; Wilkinson et al. 1989). UCHL1 constitutes 1–2% of soluble brain protein and is present in Lewy bodies (Maraganore et al. 2004). UCHL1 functions as a deubiquitinase (DUB) in ubiquitin-dependent proteolysis, a pathway responsible for damaged or misfolded proteins degradation, cell cycle progression and cell death (Ciechanover and Brundin 2003; Spataro et al. 1998). DUBs facilitate tumor suppressive function in a cascade of signaling pathway (Reyes-Turcu et al. 2009). In addition, the dimeric form of UCHL1 acts as a ligase to extend polyubiquitin chains on α-synuclein and tubulin (Bheda et al. 2010; Liu et al. 2002). Although PD pathogenesis mediated by UCHL1 ligase activity remains unclear, Liu et al. hypothesized that UCH1 promotes lysine-63 polyubiquitination and creates an elevation of α-synuclein that interrupting proteasomal degradation (Liu et al. 2002). The study also proposed that lysine-63 polyubiquitination of α-synuclein may promote pathogenic protofibrils formation and lead to neurotoxicity (Liu et al. 2002).

Even though UCHL1 is widely expressed in neurons, several studies have suggested a positive correlation between UCHL1 and lung cancer progression (Liu et al. 2003; Yao et al. 2022). In tumorigenesis, increased deubiquitination of cyclins by UCHL1 is attributed to the uncontrolled growth of somatic cells (Yao et al. 2022) (Figure 1). Increased expression of UCHL1 is detected in the lung cancer cell lines, hence it may be a potential marker for NSCLC and SCLC (Kim et al. 2009; Sasaki et al. 2001; Shimada et al. 2020). A study by Sasaki et al. showed that UCHL1 expressions were closely correlated with T-stages (features of primary tumor) of NSCLCs, but not with N-stages (regional lymph node involvement) (Sasaki et al. 2001). Thus, the results showed that UCHL1 plays a role in the early stage of lung carcinogenesis (Sasaki et al. 2001). Moreover, overexpression of UCH-L1 in lung cancer cells was reported to activate PI3K-Akt and MAPK signalling pathways. This suggests that UCH-L1 overexpression promotes cell survival and tumour progression (Hurst-Kennedy et al. 2012; Kim et al. 2009). Nevertheless, the actions of UCHL1 on lung cancer

development and invasion require further investigation to establish a better understanding of its mechanism.

LRRK2

Leucine-rich repeat kinase 2 (LRRK2) gene mutations are one of the leading causes of autosomal dominant PD (Rivero-Ríos et al. 2020; Tolosa et al. 2020). LRRK2 is a large protein (280 kDa) consisting of multiple domains including Ras of Complex (Roc) GTPase, COR (C-terminal of ROC) and other protein–protein interaction domains (Jeong and Lee 2020; Rui et al. 2018). Thus, this LRRK2 protein undergoes multifunctional activities by interacting with diverse proteins and exhibiting catalytic activities as GTPase and kinase (Ravinther et al. 2022). LRRK2 is found to be involved in various cellular processes including inflammation, autophagy, cell survival, homeostasis, protein degradation and mitochondrial functions (Funk et al. 2019). There are seven missense LRRK2 mutations namely R1441G, R1441C, R1441H, R1628P, G2019S, G2385R, I2020T and Y1699C found in PD for which G2019S mutation is the most prevalent (Rivero-Ríos et al. 2020; Rui et al. 2018). These mutations lead to gain-of-function mechanisms, where increased LRRK2 kinase phosphorylates Rab proteins at different subcellular localities, thereby affecting downstream pathways and driving towards PD pathogenesis (Berwick et al. 2019). Several studies have revealed that LRRK2 could potentially mediate α-synuclein toxicity by reducing α-synuclein clearance in microglia *via* endo-lysosomal pathway whereas LRRK2 G2019S enhances α-synuclein aggregation in neurons (Maekawa et al. 2016; Volpicelli-Daley et al. 2016). Besides, LRRK2 is an upstream regulator of mitogen activated protein kinases (MAPK), shown in both *in vivo* and *in vitro* studies. LRRK2 phosphorylates apoptosis signal-regulating kinase 1 (ASK1) and several MAPK kinases including p38 MAPK, c-Jun N-terminal kinases (JNKs) and extracellular signal-regulated kinase (ERK) and activates neuronal apoptosis (Ravinther et al. 2022; Yoon et al. 2017). In addition, LRRK2 G2019S mutation enhances the effect of LRRK2 kinase activity by inducing abnormal activation of both MAPK and JNK signaling pathways and ultimately causing neuronal cell death (Rui et al. 2018; Wallings et al. 2015). Furthermore, LRRK2 modulates autophagy in different cell types (Albanese et al. 2019). Several findings showed that LRRK2 regulates autophagy *via* MEK/ERK pathway in G2019S mutant fibroblasts (Bravo-San Pedro et al. 2013), Beclin-1/PI3K pathway in astrocytic cells (Manzoni et al. 2016), mTOR-dependent pathway in RAW264.7 macrophages or murine BV2 microglial cells (Schapansky et al. 2014) and Ca^{2+}/CaMKK/AMPK pathway in dopaminergic neuroendocrine cells and PC12 cells (Bedford et al. 2016; Gómez-Suaga and Hilfiker 2012). Of these, LRRK2 could possibly initiate another pathway in cancer cells.

A previous study has reported decreased LRRK2 expression in lung adenocarcinoma (Lebovitz et al. 2021). The study has also shown that *in vivo* LRRK2 knockdown would promote lung tumorigenesis (Lebovitz et al. 2021). As LRRK2 has been implicated in autophagic processes, studies revealed that knockout of LRRK2 could lead to excessive accumulation of proteins that are involved in the impaired induction of autophagy in kidney and lung cells (Herzig et al. 2011; Tong et al. 2010) (Figure 1). The findings revealed abnormal accumulation of secretory lysosomes called lamellar bodies in lung alveolar type II cells of nonhuman primates when LRRK2 production is inhibited (Baptista et al. 2020; Fuji et al. 2015; Herzig et al. 2011). Besides, deficiency of LRRK2 is reported to impair ERK and JNK signalling pathways which contributes to the autophagic dysfunction and cell senescence (Tian et al. 2021). However, the oncogenic mechanism of LRRK2 dysregulation and its effect in lung cancer require more investigation.

Future perspectives

An understanding of the potential roles of these PD-associated genes and their gene products in lung cancer development can be beneficial in strategizing new therapeutic options for lung cancer. For instance, gene therapy can be exploited to regulate the expression profiles of these genes. Gene therapy has been a promising approach to cancer treatment since the emergence of various high-throughput genomic technologies (Belete 2021; Roma-Rodrigues et al. 2020). One of the most widely used techniques is the recombinant DNA technology such as viral vectors, bactofection and non-viral vectors (chemical and physical) that can deliver gene products (Belete 2021). Besides, advancement in CRISPR/Cas9 genome editing technology is now being tested in clinical trials for lung cancer treatment (Nair et al. 2020). In addition, gene-editing technology is explored to combat the drug resistance in various cancers such as breast, colon, and prostate cancers (Domenici et al. 2019; Kawamura et al. 2015; Li et al. 2019). In the future, this might open a new horizon at which the adjuvant uses of gene therapy along with conventional cancer therapy may be obligatory for advanced-stage lung cancer and drug-resistant patients. Other than that, comprehensive molecular profiling of lung cancer can help establishing a precise classification of lung cancer, so it would not rely solely on the morphology and the detection of various molecular markers.

On top of that, the knowledge gained from studying these genes in lung cancer may also help to understand their physiological roles as well as their roles in the pathogenesis of PD. Genes such as LRRK2, despite being identified as a PD-associated gene, are still poorly understood in terms of their biological functions and how they differ in different cell types (Rocha et al. 2022). Therefore, investigations through lung cancer models or biopsied tumor samples might be able to yield insight to close some knowledge gaps and facilitates development of disease modifying strategies for PD treatment.

Conclusions

Although the current epidemiological studies suggest a potential negative association between PD and lung cancer, the molecular mechanisms of the shared genetic determinants between the two diseases in tumorigenesis remain unclear. The cell autonomous and cell non-autonomous gene functions in both diseases must be considered to clarify and resolve the roles of the different genes and their gene products. The evidence listed in this review have shown that proteins encoded by PD-associated genes contribute to mitochondrial dysfunction, cell cycle abnormalities, oxidative stress, cell death and various pathophysiology in both PD and lung cancer. Mutations or loss-of-function of these genes in PD result in neuro-degeneration whereas the aberrant expressions of these PD-associated genes in lung cancer cells modulate tumor-igenesis. Hence, further investigations of the PD-associated genes in lung cancer are warranted to have a better understanding on their mechanisms of action. This would help in the development of new novel targeted therapeutic strategies for lung cancer patients. Also, an in-depth understanding of these genes and their gene products might be beneficial to the development of biomarkers for early detection of lung cancer.

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