The emerging multifaceted role of PINK1 in cancer biology

Meng Wang1,2,3,4 | Shijia Luan2 | Xiang Fan2 | Jie Wang2 | Ju Huang2 | Xu Gao2 | Dong Han2,5

1Department of Colorectal Surgery, Cancer Hospital of University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China
2Department of Biochemistry and Molecular Biology, Harbin Medical University, Harbin, China
3Department of Colorectal Surgery, the Second Affiliated Hospital of Harbin Medical University, Harbin, China
4Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, USA
5Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas, USA

Correspondence
Dong Han, Department of Biochemistry and Molecular Biology, Harbin Medical University, Harbin, Heilongjiang 150081, China.
Email: handong85@163.com

Abstract
For its various important functions in cells, phosphatase and tensin homolog-induced kinase 1 (PINK1) has drawn considerable attention for the role it plays in early-onset Parkinson's disease. In recent years, emerging evidence has supported the hypothesis that PINK1 plays a part in regulating many physiological and pathophysiological processes in cancer cells, including cytoplasmic homeostasis, cell survival, and cell death. According to the findings of these studies, PINK1 can function as a tumor promoter or suppressor, showing a duality that is dependent on the context. In this study we review the mechanistic characters relating to PINK1 based on available published data from peer-reviewed articles, The Cancer Genome Atlas data mining, and cell-based assays. This mini review focuses on some of the interplays between PINK1 and the context and recent developments in the field, including its growing involvement in mitophagy and its nonmitophagy organelles-related function. This review aims to help readers better grasp how PINK1 is functioning in cell physiological and pathophysiological processes, especially in cancer biology.

KEYWORDS
antitumor, cancer, mitophagy, oncogene, PINK1

1 | INTRODUCTION

In 2001, a serine/threonine kinase that is upregulated by exogenous expression phosphatase and tensin homolog (PTEN) was discovered and named PTEN-induced kinase-1 (PINK1).1 Soon after its discovery, researchers found that the higher the metastatic potential, the higher the expression of PINK1 in cancer cell lines2 and that loss-of-function mutations in PINK1 are a contributory factor in autosomal recessive parkinsonism.3 Researchers began to study the effect of PINK1 on neuronal and other systems, especially the role it plays in cell death, mitochondrial function, and many other cellular bioenergetics.4 Gaining a better understanding of Parkinson's disease (PD) is the top priority of research on PINK1. However, as more and more research focuses on the PINK1 signaling system, it has been demonstrated that this signaling system controls several essential processes in cancer. This directs research interest to the relationship between PINK1 and cancer etiology. Research has revealed the dual role of PINK1 in cancer etiology. For example, PINK1 serves as a tumor suppressor through regulating the Warburg effect5 and iron-mediated immunometabolism,6 or as an oncogenic promoter in lung,7 breast8 and esophageal cancer,9 thereby exhibiting “antagonistic duality”. This review covers the research evidence on PINK1 in...
different cancers and gives an overview of some of the most important functions of PINK1 in cancer biology.

2 | PINK1 FUNCTION OVERVIEW

PINK1 is a putative mitochondrial serine/threonine kinase which encodes a protein containing 581 amino acids. The PINK1 protein consists of an N-terminal, noncanonical mitochondrial targeting sequence (MTS), a transmembrane domain, a highly conserved serine/threonine kinase domain, and a C-terminal autoregulatory sequence.10 In most cases, PINK1 is imported into the mitochondria, cleaved by proteases such as Presenilin Associated Rhomboid Like (PARL). The deleted N-terminal PINK1 is released by PARL cleavage into the cytosol, where the N-terminal phenylalanine produced by proteolysis is recognized by E3 enzymes in accordance with the N-end rule and degraded via the ubiquitin proteasome system.11,12 Damage to the mitochondria prevents the cleavage of proteases, then PINK1’s ubiquitin kinase activity is activated by autophosphorylation, as a result the importing of PINK1 arrests on the translocase of the outer mitochondrial membrane complex.13 The kinase domain of PINK1 is maintained on the cytosolic face of the mitochondrial outer membrane (MOM) and the N-terminal tail is inside the mitochondria.14 The structural and functional domains of the PINK1 protein are shown in Figure 1. There are three distinct insert regions, Insert 1, Insert 2, and Insert 3, in the kinase domain of PINK1.15 Several studies have revealed that Insert 3 is a key motif for PINK1 to recognize and attach to the phosphorylation site during PINK1 autophosphorylation, and then Insert 3 binds to PINK1’s substrates such as ubiquitin.16

In 2001, it was discovered that the PINK1 gene is a PTEN target,4 and in 2004, it was found that early-onset PD and PINK1 have a significant mitochondrial link.3 Mature PINK1 can be liberated into the cytosol or the intermembrane space of the mitochondria. Mitophagy can be triggered by targeting this precursor to the outer mitochondrial membrane.17 It was shown that autophagy receptors are recruited by the ubiquitin kinase PINK1 to induce mitophagy.18 The loss of PINK1 impairs mitochondrial function and increases oxidative stress sensitivity.19 At present, PINK1 has a pivotal role in mitochondrial quality control via the mitochondrial stabilization and phosphorylation of chaperones.

3 | PINK1 AND CANCER OVERVIEW

The primary progress of PINK1 research has been to better understand PD.20 The majority of the genes connected to PD are also linked to malignancy.21 Despite the fact that PD and cancer are clearly dissimilar human disorders, evidence suggests that cancer rates among PD patients are low, possibly due to the common pathways in both diseases.22 Epidemiological studies back up this correlation between cancer and neurodegeneration, indicating that patients with neurodegenerative diseases like PD have a lower risk of certain cancers.23 Importantly, PINK1 was discovered to cause inherited PD, and it has been suggested that it has oncogenic tumor suppressive capabilities.21

PINK1 has anti-apoptotic and cytoprotective effects, according to research conducted over the last decade.24 PINK1 has been speculated to have a dual role in cancer biology, having pro- and anti-tumorigenic characters that vary depending on the context. This is corroborated by analysis of PINK1 expression in the Human Protein Atlas (https://www.proteinatlas.org/), which states that PINK1 can be beneficial or harmful depending on the cancer type. For example, PINK1 predicted improved overall survival (OS) in liver, renal, pancreatic, and endometrial cancer (Figure 2), but poor prognosis in breast, cervical, ovarian, lung cancer, glioma, and melanoma (Figure 3), with the protein immunolocalized to the cytoplasmic compartment in tissue microarrays (Figures 2 and 3). According to data from The Cancer Genome Atlas (TCGA), PINK1 “high” expression was linked to a better prognosis for malignancies of the kidney and uterus (Figure 4). However, for lung, esophagus, and ovarian malignancies, “low” PINK1 expression was related to a better overall survival rate (Figure 4).

4 | PINK1 REGULATION OF MITOPHAGY IN CANCER

Mitochondrial malfunction has been linked to a variety of human illnesses, including cancer. During carcinogenesis, mitochondria undergo a range of morphological and functional alterations. Cellular transformation is a multistep process that may demand an ad hoc sequence of genomic changes and intracellular signaling changes.25 Transformed cells’ metabolic profiles are altered to enable their proliferation, confer resistance to cell death, or facilitate metastasis. The transformation mechanisms may open new possibilities for the treatment of cancer at different stages.

4.1 | Multifaced role of PINK1 in regulating mitophagy in cancer

Interestingly, several researchers have reported that many alkaloids or natural medicines with antitumor potential affect the biofunctions of mitochondria in cancer cells through inducing mitochondria-dependent apoptosis, autophagy or inhibition of mitochondrial metabolic processes. BSG1, a novel derivative of betulinic acid, for example, causes cell death in multidrug-resistant cancer cells via the mitochondrial-apoptosis route, according to Yao et al. They demonstrated that BSG1 upregulates PINK1 to recruit Parkin to mitochondria, then ubiquitinates Mfn2 to induce mitophagy. However, the role of mitophagy induced by BSG1-PINK1 depends on cell types and chemical structures.26 Wei et al. showed that matrine increases apoptosis in liver cancer cells by suppressing the PINK1/mitophagy pathways.27 In addition, polyphyllin I was reported to induce mitophagic and apoptotic cell death by stabilization of full-length PINK1 at the mitochondrial surface.28
However, mitophagy has double faces in tumorigenesis: depending on the cellular microenvironment, it either supports cell survival or contributes to cell death. For instance, Villa and colleagues reported that E3 ubiquitin ligase ARIH1 protects cancer cells from chemotherapy-induced death through triggering mitophagy in a PINK1-dependent manner. Furthermore, studies have demonstrated that in neuroblastoma cells, manganese (Mn), an environmental risk factor of PD that is thought to induce manganism, protects dopaminergic neuronal cells from death by triggering PINK1/Parkin-mediated mitophagy. Additionally, one of the heavier pnictogens, antimony, contributes to cancer by inhibiting the PINK1/Parkin pathway-controlled process of mitophagy. These observations indicate that the function of PINK1 in regulating mitophagy might be a double-edged sword for cancer. Further detailed studies are needed to uncover the exact potential clinical significance of PINK1.

### 4.2 PINK1-mediated mitophagy activated by ROS

Reactive oxygen species (ROS) induces DNA damage, which has well-documented pathological consequences, including cancer. Separate from the idea that oxidative DNA damage initiates cell transformation, current research has found that mitochondrial deficits affect cell proliferation after cell transformation. Recently, several reports have also demonstrated that ROS activated PINK1/Parkin-mediated mitophagy. For example, research from Zhao showed that in pancreatic cancer cells, Rocaglamide A induces apoptosis through PINK1-mediated mitophagy regulation by ROS. Multiple cancer cell types have been found to be targeted by zinc oxide nanoparticles (ZnO NPs). Wang’s recent research found that ZnO NPs enhanced ROS while reducing the mitochondrial membrane potential, triggering PINK1/Parkin-mediated mitophagy and potentially inducing cancer cell death. Park et al. showed that Parkin recruitment from the cytosol to the dysfunctional mitochondria was increased after chlorpyrifos treatment because PINK1 was stabilized on the outer mitochondrial membrane. Furthermore, Yu et al. reported that ionizing radiation promotes autophagic death in MCF-7 and HeLa cells, which is associated with the generation of mitochondrial reactive oxygen species (mROS) and dependent on the PINK1/PARK2 pathway. This kind of approach together with the detailed mechanism involved remains to be further explored.

### 4.3 PINK1 works together with p53 to control mitophagy

p53 is a critical protein with a role in numerous diseases that has been widely researched. It is a transcription factor that can regulate many genes involved in cell death/survival mechanisms, such as
FIGURE 3  (A–C) and (G–I) Overall survival (OS) in breast, cervical, ovarian, lung cancer, melanoma, and glioma patients with high vs. low PINK1 mRNA expression in tumors. (D–F) and (J–L) Immunodetection of PINK1 for the corresponding tumor types shown in A–C and G–I. Immunohistochemistry images were obtained from the Human Protein Atlas (https://www.proteinatlas.org/).
apoptosis and autophagy, either positively or negatively. The fact that p53-dependent autophagy control is directly controlled by its subcellular location is widely accepted. A functional interaction between p53 and Parkin has been demonstrated in several studies. Parkin and p53, by their DNA binding characteristics, influence each other’s transcription in physiological settings. Parkin has been found to be attracted to mitochondria and activated by PINK1 on its phosphorylation, and to be implicated in the degradation of various hazardous proteins by the proteasome via its ubiquitin-ligase activity. The fact that p53 and Parkin are related led us to believe that p53 and PINK1 are coupled at a molecular level to control mitophagy. Recently, research from Goiran has demonstrated that nuclear p53 binds to PINK1 promoter and represses its activity, and then represses PINK1 gene transcription, which is independent of Parkin. These data demonstrate that PINK1 is essential for p53-induced autophagy suppression.

5 | NONMITOPHAGY MECHANISMS OF PINK1 IN CANCERS

While mitophagy dominates the scholarly literature on PINK1 for historical reasons, other events have been linked to this eclectic kinase. PINK1 and its elusive additional associated functions emerged quickly. PINK1 is suggested to play a dual role in cancer biology, having pro- or antitumorigenic capabilities depending on the situation.

5.1 | Tumor promotor properties of PINK1

Multiple investigations have explored the expression of PINK1 in various human cancers and their clinical outcomes, finding evidence for oncogenic involvement in some cases and a tumor suppressor role in others (Table 1). Molecular analyses have implicated a diverse array of protein partners (Figure 5).

In lung cancer and esophageal squamous cell carcinoma (ESCC), a tumor-promoting role for PINK1 has been hypothesized based on loss of heterozygosity. Immunohistochemical analysis was conducted to detect PINK1 expression in 256 nonsmall-cell lung cancer (NSCLC) patients, including 137 patients with adenocarcinoma (AC) and 119 patients with squamous cell carcinoma (SCC). It was found that high PINK1 expression is linked to a poor treatment response and is an independent prognostic factor for AC, but not for SCC. Similarly, another study found greater PINK1 expression in tumor tissues in 87 matched NSCLC tissues. Low PINK1 expression levels were also related to considerably longer overall survival in a study of 1085 NSCLC patients. The same result was detected from 217 ESCC patients in Yamashita’s research. These results suggest a possible role for PINK1 in lung oncogenesis.

In cell-based assays, research associated with breast cancer demonstrated that PINK1 promotes cancer-related traits by acting as a positive regulator of cell cycle progression. This is the first time that PINK1 modulation of mitochondrial fission to fusion transitions has been demonstrated to be important for cell cycle progression at the G2/M and G0/G1 checkpoints, which are required for cell

FIGURE 4 Results from The Cancer Genome Atlas database indicating overall patient survival. (A–C) High PINK1 expression (red lines) predicted poor survival outcomes in esophageal cancer, lung squamous cell carcinoma, and ovarian serous cystadenocarcinoma. (D–F) High PINK1 expression (red lines) predicted favorable survival in kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, and uterine corpus endometrial carcinoma.
| Cancer type                          | Samples                                      | Potential mechanism                                                                 | Function in tumorigenesis                                                                 | Reference |
|------------------------------------|----------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-----------|
| Breast and liver cancer            | HepG2, MCF-7                                 | Inhibition of PINK1/Parkin-dependent mitophagy sensitizes multidrug-resistant cancer cells to BSG1 | PINK1/Parkin-mediated mitophagy                                                          | 26        |
| Pancreatic cancer                  | PANC-1, MIA PaCa2, TKF-1, HepG2, HCT-116, LO2, HK-2 | PINK1/Parkin-mediated mitophagy regulation by ROS alleviates rocaglamide A-induced apoptosis | PINK1/Parkin-mediated mitophagy                                                          | 33        |
| Hepatocellular carcinoma           | HepG2                                        | Matrine promotes liver cancer cell apoptosis by inhibiting mitophagy and the PINK1/Parkin pathway | PINK1/Parkin-mediated mitophagy                                                          | 27        |
| Breast cancer                      | MDA-MB-231 (HTB-26) and MCF-7                | Polyphylin I induces mitophagic and apoptotic cell death by stabilization of full-length PINK1 at the mitochondrial surface | PINK1/Parkin-mediated mitophagy                                                          | 28        |
| Brain cancer                       | U87MG and T98G cells                         | SIRT1 activator Comp 5 induces mitophagy by the SIRT1-PINK1-Parkin pathway           | PINK1/Parkin-mediated mitophagy                                                          | 65        |
| Multiple cancers                   | PC-3 and MDA-MB-231                          | Chalocomoracin upregulates PINK1 mitophagy signaling, the novel pathway is triggered by ROS production | PINK1/Parkin-mediated mitophagy                                                          | 66        |
| Tongue squamous cell carcinoma     | 27 cell lines                                | ZnO nanoparticles increase ROS and decrease the mitochondrial membrane potential, activating PINK1/Parkin-mediated mitophagy | PINK1/Parkin-mediated mitophagy                                                          | 34        |
| Neuroblastoma cells                | SH-SY5Y                                      | Mn induces PINK1/Parkin-mediated mitophagy, exerting a neuroprotective effect against Mn-induced dopaminergic neuronal cells apoptosis | PINK1/Parkin-mediated mitophagy                                                          | 30        |
| Neuroblastoma cells                | SH-SY5Y                                      | Chloropyrifos treatment results in PINK1 stabilization on the outer mitochondrial membrane and subsequently increases Parkin recruitment from the cytosol to the abnormal mitochondria | PINK1/Parkin-mediated mitophagy                                                          | 35        |
| Multiple cancers                   | MCF-7, HeLa                                  | Mitophagy induced by mROSA can initiate the sensitization of cancer cells to ionizing radiation through the Pink1/PARK2 pathway | PINK1/Parkin-mediated mitophagy                                                          | 36        |
| Osteosarcoma                       | Saos-2 and MG-63                             | Parthenolide (molecule interferes with NF-Kb signaling) increases the autophagy and mitophagy, as characterized by increased PINK1 and Parkin translocation to mitochondria and enhanced autophagy | PINK1/Parkin-mediated mitophagy                                                          | 67        |
| Bladder cancer                     | EJ cell, nude mice, and patient serum sample | Antimony has its carcinogenic effect by inhibiting mitophagy dependent on the PINK1/Parkin pathway | PINK1/Parkin-mediated mitophagy                                                          | 31        |
| Multiple cancers                   | MEF, HCT116, SH-SY5Y, HEK293                 | P53-mediated negative regulation of autophagy is PINK1-dependent, nuclear p53 controls PINK1 by repressing its promoter activity, and protein and mRNA levels | p53-PINK1-mitophagy                                                                      | 41        |
| Hepatic cancer stem cells          | Cell lines, transgenic mice, and patient samples | PINK1 binds to p53 on mitochondria and phosphorylates p53 at serine-392, PINK1-activated p53 is localized to the nucleus when mitophagy is impaired | p53-PINK1-mitophagy                                                                      | 68        |
| Cancer type                        | Samples                                                                 | Potential mechanism                                                                 | Function in tumorigenesis                        | Reference |
|-----------------------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------|-----------|
| Breast and lung cancer            | Cell lines, transgenic mice, and patient samples                        | ARIH1 controls mitophagy of damaged mitochondrial in a PINK1-dependent manner, protects cancer cells from chemotherapy-induced death | PINK1/ARIH1-mediated mitophagy                   | 29        |
| Colorectal cancer                 | 20 pairs of tumor samples                                               | PINK1 is silenced in Colorectal cancer (CRC) adenocarcinoma in comparison to control  | Tumor suppressor                                 | 69        |
| Colorectal cancer                 | MC38, PINK1 knockout mice                                               | PINK1 suppresses colon tumor growth by metabolic reprogramming via p53 activation and reducing acetyl-CoA production | Tumor suppressor                                 | 46        |
| Hepatocellular carcinoma          | PLC/PRF/5, HepG2, and Hep3B                                             | Underexpression of PINK1 is detected in human HCC and associated with poor clinical outcomes | Tumor suppressor                                 | 48        |
|                                    |                                                                         | Knockdown of PINK1 reduces mitochondrial mass and increases HCC growth (hypoxia/HIF/HEY1/PINK1/mitophagy) |                                                 |           |
| Pancreatic cancer                 | Cell lines and transgenic mice                                          | PINK1 suppresses pancreatic tumorigenesis through control of mitochondrial iron-mediated immunometabolism | Tumor suppressor                                 | 6         |
| Glioblastoma                      | Fetal human astrocytes, U87 and T98G cell lines, NOD-SCID mice          | PINK1 negatively regulates the Warburg effect and the growth of glioblastoma cells | Tumor suppressor                                 | 5         |
| Lung cancer                       | Cell lines, BALB/c nu/nu mice                                          | PINK1-CTD suppresses Epidermal growth factor receptor (EGFR) dimerization, activation and EGFR signaling, impedes EGFR-driven tumorigenesis | Tumor suppressor                                 | 47        |
| Lung cancer                       | H1299 and SPC-A-1, nude mice                                           | PINK1 suppression enhances apoptosis rate, the expression of Bax, deaved caspase 3, and poly ADP ribose polymerase (PARP), decreased migration and invasion abilities | Oncogene                                        | 70        |
| Lung cancer                       | 256 patients with nonsmall-cell lung cancer                           | High PINK1 expression is correlated with poor response to chemotherapy and is an independent prognostic factor for adenocarcinoma, but not for squamous cell carcinoma | Oncogene                                        | 7         |
| Multiple cancers                  | PINK1 knockout mice and derived MEF cell lines, MEFs, MCF-7, and HeLa | PINK1 regulates cell cycle progression, reduced cancer associated phenotypes, including cell proliferation, colony formation, and invasiveness | Oncogene                                        | 8         |
| Esophageal squamous cell carcinoma| 217 ESCC patients                                                      | High expression of PINK1 is associated with chemoresistance and a poor prognosis for ESCC patients undergoing neoadjuvant chemotherapy | Oncogene                                        | 9         |
| Lung cancer                       | 87 paired nonsmall-cell lung cancer tissues, A549 and H1975            | PINK1 overexpression promotes cell migration and proliferation via regulation of autophagy and predicts a poor prognosis in lung cancer cases | Oncogene                                        | 42        |
| Breast cancer                     | MDA-MB-231, transgenic mice                                            | PINK1 drives production of Mitochondrial DNA (mtDNA)-containing extracellular vesicles to promote invasiveness by activating Toll-like receptor 9 in recipient cells | Oncogene                                        | 43        |

Abbreviations: EGFR, epidermal growth factor receptor; ESCC, esophageal squamous cell carcinoma; HCC, human hepatocellular carcinoma; ROS, reactive oxygen species.
division, growth, and stress tolerance in cancer biology. Recently, other research has shown that PINK1 participated in the packaging of mitochondrial DNA (mtDNA) into extracellular vesicles, suggesting that mitophagy and mitochondrial DNA (mtDNA)-containing extracellular vesicles (EV) production may share features. Furthermore, in lung cancer cell lines H1299, SPC-A-1, A549, and H1975, it was showed that PINK1 suppression enhanced apoptosis rate, the expression of Bax, cleaved caspase-3 and poly ADP ribose polymerase (PARP), and decreased cell migration and invasion abilities. These results imply that the development of lung cancer may be accompanied by increased expression of PINK1.

5.2 | Tumor suppressor properties of PINK1

To adapt to the tumor environment, cancer cells exhibit aerobic glycolysis or the Warburg effect, abnormal mitochondrial quality control, modification of cellular redox state, ROS production, and creation of apoptotic signals. Mitophagy has been shown to play a role in either promoting or inhibiting carcinogenesis, and its failure contributes to oncogenic stress and tumorigenesis. Accordingly, PINK1 was recently reported exhibiting tumor suppressor roles in cancer. For example, research associated with pancreatic cancer demonstrated that mitophagy mediated by PINK1 degrades iron importers such as SLC25A37 and SLC25A28, resulting in mitochondrial iron accumulating. Similarly, PINK1 reduces the formation of glioblastomas by controlling aerobic glycolysis, ROS, and mitochondrial oxidative phosphorylation. This observation supports the notion that PINK1 may inhibit the proliferation capability of glioblastoma. Further studies suggest that PINK1 overexpression accelerated mitophagy, decreased glycolysis, and increased mitochondrial respiration in mouse colon carcinoma cells by activating p53 signaling pathways. Through the PINK1 C-terminal domain (PINK1-CTD) and the Epidermal growth factor receptor (EGFR) tyrosine kinase domain, PINK1 physically interacts with Epidermal growth factor receptor (EGFR). This relationship prevents EGFR-mediated lung carcinogenesis by acting as an endogenous steric restriction to receptor dimerization. Interestingly, in contrast to the tumor-promoting properties of PINK1 in lung cancer or esophageal squamous cell carcinoma, PINK1 underexpression has been found in human hepatocellular carcinoma and has been linked to poor clinical outcomes. Taken together, these data indicate the tumor suppression effect of PINK1.

6 | POSTTRANSCRIPTIONAL MODIFICATIONS AFFECTING PINK1 DUALITY

Genetic and epigenetic changes can affect the mechanisms of PINK1 regulation mentioned above. It is now well established that extensive posttranslational modifications such as phosphorylation/ dephosphorylation, methylation/demethylation, and acetylation/deacetylation play an important role in the exact signaling pathway. Parkin, an E3 ligase whose function is explained below, has been found to be phosphorylated by PINK1 in its ubiquitin (Ub)-like (UBL) domain (Ser65), and this phosphorylation is important for Parkin’s mitochondrial recruitment and E3 ligase activity. The Ser65 site on Ub, which is identical to Parkin at Ser65 in the UBL domain, is phosphorylated by PINK1 in response to mitochondrial depolarization. This kind of posttranslational alteration is essential for Parkin-activated cells. PINK1 phosphorylates Ser65 in both the ubiquitin and ubiquitin-like (UBL) domains of Parkin, which stimulates its E3 ligase activity. Autophosphorylation of PINK1 is required for Parkin activation. Parkin and ubiquitin have been shown to be substrates of PINK1 by independent research spanning several different fields. Other substrates of PINK1 were identified recently, such as mitofusin 2 (MFN2) and MIRO (RHOT). In addition, in a novel brain cell-specific manner, HDAC3 was reported to be phosphorylated by PINK1 at Ser-424. However, the significance of those substrates is less clear, so their conclusion is needed to be proven by further independent studies.

There is some research focused on the 5′-cytosine-phosphate-guanine-3′ (CpG) islands of PINK1 promoter and the methylation status of PINK1 expression in human cancers. However, Tarale et al. performed manganese-exposed human neuroblastoma SH-SY5Y cells’ global DNA methylation profiling then highly DNA methylation status on PINK1 promoter was found, which may indicate how the mitochondrial function was influenced. Recent studies implicating noncoding RNAs are gaining attention in the context of PINK1 signaling. For example, the Autophagy-related circular RNA (ACR) was found to activate PINK1 expression by directly binding to Dnmt3B, after which PINK1 is phosphorylated at serine 46 to inhibit autophagy and cell death. It is commonly acknowledged that miRNAs have a role in the control of PINK1 signaling. Downregulation of miR-155, miR-421, and miR-27b has been documented by targeting the 3′ untranslated regions (3′ UTRs) in PINK1 mRNA. Furthermore, several long noncoding RNAs were reported to regulate PINK1 signaling and play a biological role in Alzheimer’s disease, diabetic disease, and PD, but no relevance was found in human cancers.

7 | CONCLUSIONS

Because of its yin/yang roles in prevention and promotion (Figure 5), PINK1 is a complicated regulator in cancer etiology, governed in part by early versus late phases of disease pathogenesis. PINK1 could be a potential target for cancer prevention or a biomarker for predicting cancer therapy response, especially for energy therapies that are resistant to chemotherapy, DNA damage response, or rely on mitochondrial or autophagy processes. To better understand disease mechanisms and determine the therapeutic effects of PINK1 inhibition on malignancies, more research into PINK1 and its function in cancer biology is urgently needed. In conclusion, this review depicts the reality of PINK1 as a dynamically regulated protein that has a variety of roles in tumor promotion and inhibition (Table 1).
Despite preclinical, human translational, and mechanistic evidence, the underlying mechanism and functional potential of PINK1 have yet to be fully established. This review should stimulate additional research into PINK1 as a potential master regulator of metabolism, aging, and cancer.

**AUTHOR CONTRIBUTIONS**

Meng Wang and Shijia Luan collected the data and wrote the manuscript. Xiang Fan, Jie Wang, and Ju Huang analyzed the data and revised the manuscript; Xu Gao and Dong Han wrote and revised the manuscript.
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CONFLICT OF INTEREST
The authors declare no conflict of interest.

ORCID
Dong Han https://orcid.org/0000-0003-4009-8172

REFERENCES
1. Unoki M, Nakamura Y. Growth-suppressive effects of BPOZ and EGR2, two genes involved in the PTEN signaling pathway. Oncogene. 2001;20:4457-4465.
2. Nakajima A, Kataoka K, Hong M, Sakaguchi M, Huh NH. BRPK, a novel protein kinase showing increased expression in mouse cancer cell lines with higher metastatic potential. Cancer Lett. 2003;201:195-201.
3. Valente EM, Abou-Sleiman PM, Caputo V, et al. Hereditary early-onset Parkinson’s disease caused by mutations in PINK1. Science. 2004;304:1158-1160.
4. Anichtchik O, Diekmann H, Fleming A, Roach A, Goldsmith P, Rubinsztein DC. Loss of PINK1 function affects development and results in neurodegeneration in zebrafish. J Neurosci. 2008;28:8199-8207.
5. Agnihotri S, Golbourn B, Huang X, et al. PINK1 is a negative regulator of mito- and the Warburg effect in glioblastoma. Cancer Res. 2016;76:4708-4719.
6. Li C, Zhang Y, Cheng X, et al. PINK1 and PAR2 suppress pancreatic cancer tumorigenesis through control of mitochondrial iron-mediated immunometabolism. Dev Cell. 2018;46:441-455.
7. Chang G, Zhang W, Ma Y, Wen Q. PINK1 expression is associated with poor prognosis in lung adenocarcinoma. Tohoku J Exp Med. 2018;245:115-121.
8. O’Flanagan CH, Morais VA, Wurst W, De Strooper B, O’Neill C. The Parkinson’s gene PINK1 regulates cell cycle progression and promotes cancer-associated phenotypes. Oncogene. 2015;34:1363-1374.
9. Yamashita K, Miyata H, Makino T, et al. High expression of the mitophagy-related protein PINK1 is associated with a poor response to chemotherapy and a poor prognosis for patients treated with neoadjuvant chemotherapy for esophageal squamous cell carcinoma. Ann Surg Oncol. 2017;24:4025-4032.
10. Cardona F, Sanchez-Mut JV, Dopazo H, Perez-Tur J. Phylogenetic and in silico structural analysis of the Parkinson disease-related kinase PINK1. Hum Mutat. 2011;32:369-378.
11. Yamano K, Youle RJ. PINK1 is degraded through the N-end rule pathway. Autophagy. 2013;9:1758-1769.
12. Pickrell AM, Youle RJ. The roles of PINK1, parkin, and mitochondrial fidelity in Parkinson’s disease. Neuron. 2015;85:257-273.
13. Rasool S, Soya N, Truong L, Croteau N, Lukacs GL, Trempe JF. PINK1 autophosphorylation is required for ubiquitin recognition. EMBO Rep. 2018;19(4):e44981.
14. Zhou C, Huang Y, Shao Y, et al. The kinase domain of mitochondrial PINK1 faces the cytoplasm. Proc Natl Acad Sci USA. 2008;105:12022-12027.
15. Onishi M, Yamano K, Sato M, Matsuda N, Okamoto K. Molecular mechanisms and physiological functions of mitophagy. EMBO J. 2021;40:e104705.
16. Schubert AF, Gladkova C, Pardon E, et al. Structure of PINK1 in complex with its substrate ubiquitin. Nature. 2017;552:51-56.
17. Okatsu K, Oka T, Iguichi M, et al. PINK1 autophosphorylation upon membrane potential dissipation is essential for parkin recruitment to damaged mitochondria. Nat Commun. 2012;3:1016.
18. Lazaro M, Sliter DA, Kane LA, et al. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. Nature. 2015;524:309-314.
19. Gautier CA, Kitada T, Shen J. Loss of PINK1 causes mitochondrial functional defects and increased sensitivity to oxidative stress. Proc Natl Acad Sci USA. 2008;105:11364-11369.
20. Pogson JH, Ivatt RM, Whitworth AJ. Molecular mechanisms of PINK1-related neurodegeneration. Curr Neurol Neurosci Rep. 2011;11:283-290.
21. Garber K. Parkinson's disease and cancer: the unexplored connection. J Natl Cancer Inst. 2010;102:371-374.
22. Kalyanaraman B. Teaching the basics of repurposing mitochondria-targeted drugs: from Parkinson’s disease to cancer and back to Parkinson’s disease. Redox Biol. 2020;36;101665.
23. Tabares-Seisdedos R, Rubenstein JL. Inverse cancer comorbidity: a serendipitous opportunity to gain insight into CNS disorders. Nat Rev Neurosci. 2013;14:293-304.
24. Arena G, Gelmetti V, Torosantucci L, et al. PINK1 protects against cell death induced by mitochondrial depolarization, by phosphorylating Bcl-xL and impairing its pro-apoptotic cleavage. Cell Death Differ. 2013;20:920-930.
25. Sen S, Hopwood V. Molecular cytogenetic evidence for multistep tumorigenesis: implications for risk assessment and early detection. Cancer Biomark. 2010;9:113-132.
26. Yao N, Wang C, Hu N, et al. Inhibition of PINK1/parkin-dependent mitophagy sensitizes multidrug-resistant cancer cells to BSG1, a new betulinic acid analog. Cell Death Dis. 2018;9(4):e44982.
27. Wei R, Cao J, Yao S. Matrine promotes liver cancer cell apoptosis by inhibiting mitophagy and PINK1/parkin pathways. Cell Stress Chaperoners. 2018;23:1295-1309.
28. Guo-Bing Li R-QF, Shen H-M, Zhou J, et al. Polyphylalin induces mitophagic and apoptotic cell death in human breast cancer cells by increasing mitochondrial PINK1 levels. Oncotarget. 2017;8:10359-10374.
29. Villa E, Proics E, Rubio-Patino C, et al. Parkin-independent mitophagy controls chemotherapeutic response in cancer cells. Cell Rep. 2017;20:2846-2859.
30. Zhang HT, Mi L, Wang T, et al. PINK1/parkin-mediated mitophagy play a protective role in manganese induced apoptosis in SH-SY5Y cells. Toxicol in Vitro. 2016;34:212-219.
31. Lou Y, Ma C, Liu Z, et al. Antimony exposure promotes bladder tumor cell growth by inhibiting PINK1-parkin-mediated mitophagy. Ecotoxicol Environ Saf. 2021;221:112420.
32. Casalena G, Daehn I, Bottinger E. Transforming growth factor-beta, bioenergetics, and mitochondria in renal disease. Semin Nephrol. 2012;32:295-303.
33. Zhao C, He R, Shen M, et al. PINK1/parkin-mediated mitophagy regulation by reactive oxygen species alleviates Rocaglamide A-induced apoptosis in pancreatic cancer cells. Front Pharmacol. 2019;10:968.
34. Wang J, Gao S, Wang S, Xu Z, Wei L. Zinc oxide nanoparticles induce toxicity in CAL 27 oral cancer cell lines by activating PINK1/parkin-mediated mitophagy. Int J Nanomed. 2018;13:3441-3450.
35. Park JH, Ko J, Park YS, Park J, Hwang J, Koh HC. Clearance of damaged mitochondria through PINK1 stabilization by JNK and ERK
MAPK signaling in chlorpyrifos-treated neuroblastoma cells. Mol Neurobiol. 2017;54:1844-1857.

36. Yu L, Yang X, Li X, et al. Pink1/PARK2/mROS-dependent mitophagy initiates the sensitization of cancer cells to radiation. Oxid Med Cell Longev. 2021;2021:5595652-5595613.

37. Maiuri MC, Galluzzi L, Morelli E, Kepp O, Malik SA, Kroemer G. Autophagy regulation by p53. Curr Opin Cell Biol. 2010;22:181-185.

38. da Costa CA, Sunyach C, Giaime E, et al. Transcriptional repression of p53 by parkin and impairment by mutations associated with autosomal recessive juvenile Parkinson’s disease. Nat Cell Biol. 2009;11:1370-1375.

39. Shimura H, Hattori N, Kubo S, et al. Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase. Nat Genet. 2000;25:302-305.

40. Shiba-Fukushima K, Imai Y, Yoshida S, et al. PINK1-mediated phosphorylation of the parkin ubiquitin-like domain primes mitochondrial translocation of parkin and regulates mitophagy. Sci Rep. 2012;2:1002.

41. Goiran T, Duplan E, Rouland L, et al. Nuclear p53-mediated repression of autophagy involves PINK1 transcriptional down-regulation. Cell Death Differ. 2018;25:873-884.

42. Lu X, Liu QX, Zhang J, et al. PINK1 overexpression promotes cell migration and proliferation via regulation of autophagy and predicts a poor prognosis in lung cancer cases. Cancer Manag Res. 2020;12:7703-7714.

43. Rabas N, Palmer S, Mitchell L, et al. PINK1 drives production of mtDNA-containing extracellular vesicles to promote invasiveness. J Cell Biol. 2021;220(12):e202006049.

44. Naik PP, Birbrair A, Bhutia SK. Mitophagy-driven metabolic switch reprograms stem cell fate. Cell Mol Life Sci. 2019;76:27-43.

45. Chang JY, Yi HS, Kim HW, Shong M. Dysregulation of mitophagy dimerization and activation impedes EGFR-driven lung tumorigenesis. Cancer Res. 2020;205:143-153.

46. Yin K, Lee J, Liu Z, et al. Mitophagy protein PINK1 suppresses colon tumor growth by metabolic reprogramming via p53 activation and reducing acetyl-CoA production. Cell Death Differ. 2021;28:2421-2435.

47. Lin EP, Huang BT, Lai WY, et al. PINK1-mediated inhibition of EGFR dimerization and activation impedes EGFR-driven lung tumorigenesis. Cancer Res. 2021;81:1745-1757.

48. Kung-Chun Chiu D, Pui-Wah Tse A, Law CT, et al. Hypoxia regulates the mitochondrial activity of hepatocellular carcinoma cells through HIF/HEY1/PINK1 pathway. Cell Death Dis. 2019;10:934.

49. Shiba-Fukushima K, Arano T, Matsumoto G, et al. Phosphorylation of mitochondrial polyubiquitin by PINK1 promotes parkin mitochondrial tethering. PLoS Genet. 2014;10:e1004861.

50. Harris RB, Martin RJ. Site of action of putative lipostatic factor: food intake and peripheral pentose shunt activity. Am J Physiol. 1990;259:R45-R52.

51. Kane LA, Lazarou M, Fogel AI, et al. PINK1 phosphorylates ubiquitin to activate parkin E3 ubiquitin ligase activity. J Cell Biol. 2014;204:143-153.

52. Rasool S, Trempe JF. New insights into the structure of PINK1 and the mechanism of ubiquitin phosphorylation. Crit Rev Biochem Mol Biol. 2018;53:515-534.

53. Bayne AN, Trempe JF. Mechanisms of PINK1, ubiquitin and parkin interactions in mitochondrial quality control and beyond. Cell Mol Life Sci. 2019;76:4589-4611.

54. Kondapalli C, Kazlauskaitė A, Zhang N, et al. PINK1 is activated by mitochondrial membrane potential depolarization and stimulates parkin E3 ligase activity by phosphorylating serine 65. Open Biol. 2012;2:120080.

55. Dasgupta A, Chen KH, Lima PDA, et al. PINK1-induced phosphorylation of mitofusin 2 at serine 442 causes its protosomal degradation and promotes cell proliferation in lung cancer and pulmonary arterial hypertension. FASEB J. 2021;35:e21771.

56. Shlevkov E, Kramer T, Schapansky J, LaVoie MJ, Schwarz TL. Miro phosphorylation sites regulate parkin recruitment and mitochondrial motility. Proc Natl Acad Sci USA. 2016;113:E6097-E6106.

57. Choi HK, Choi Y, Kang H, et al. PINK1 positively regulates HDAC3 to suppress dopaminergic neuronal cell death. Hum Mol Genet. 2015;24:1127-1141.

58. Farouk R, Sivanesan S, Daiwile AP, et al. Global DNA methylation profiling of manganese-exposed human neuroblastoma SH-SY5Y cells reveals epigenetic alterations in Parkinson’s disease-associated genes. Arch Toxicol. 2017;91:2629-2641.

59. Zhou LY, Zhai M, Huang Y, et al. The circular RNA ACR attenuates myocardial ischemia/reperfusion injury by suppressing autophagy via modulation of the Pink1/FAM65B pathway. Cell Death Differ. 2019;26:1299-1315.

60. Tsujimoto T, Mori T, Houri K, et al. miR-155 inhibits mitophagy through suppression of BAG5, a partner protein of PINK1. Biochem Biophys Res Commun. 2020;523:707-712.

61. Chen J, Yu W, Ruan Z, Wang S. TUG1/miR-421/PINK1: a potential mechanism for treating myocardial ischemia-reperfusion injury. Int J Cardiol. 2019;292:197.

62. Ruan Z, Wang S, Yu W, Deng F. LncRNA NEAT1 aggravates diabetic myocardial ischemia-reperfusion injury through regulating PINK1 by targeting miR-27b. Int J Cardiol. 2019;286:136.

63. Huang Z, Zhao J, Wang W, Zhou J, Zhang J. Depletion of LncRNA NEAT1 rescues mitochondrial dysfunction through NEDD4L-dependent PINK1 degradation in animal models of Alzheimer’s disease. Front Cell Neurosci. 2020;14:28.

64. Yan W, Chen ZY, Chen JQ, Chen HM. LncRNA NEAT1 promotes autophagy in MPTP-induced Parkinson’s disease through stabilizing PINK1 protein. Biochem Biophys Res Commun. 2018;496:1019-1024.

65. Yao QZ, Zhang X, Zhen Y, et al. A novel small-molecule activator of Sirtuin-1 induces autophagic cell death/mitophagy as a potential therapeutic strategy in glioblastoma. Cell Death Dis. 2018;9:767.

66. Han H, Chou CC, Li R, et al. Chalcomoracin is a potent anticancer agent acting through triggering oxidative stress via a mitophagy-and paraptosis-dependent mechanism. Sci Rep. 2018;8:9566.

67. Yang C, Yang QQ, Kong QJ, Yuan W, Ou Yang YP. Parthenolide induces reactive oxygen species-mediated autophagic cell death in human osteosarcoma cells. Cell Physiol Biochem. 2016;40:146-154.

68. Liu K, Lee J, Kim JY, et al. Mitophagy controls the activities of tumor suppressor p53 to regulate hepatic cancer stem cells. Mol Cell. 2017;68:281-292.

69. Bednarczyk MM-WM, Waniczek D, Fatyga E, Klakla K, Mazurek U, Wierzcioń J. Autophagy-related gene expression in colorectal cancer patients. J Biol Regul Homeost Agents. 2017;31:923-927.

70. Liu L, Zuo Z, Lu S, Wang L, Liu A, Liu X. Silencing of PINK1 represses cell growth, migration and induces apoptosis of lung cancer cells. Bioimed Pharmacother. 2018;106:333-341.