Review

Deciphering the dual role and prognostic potential of PINK1 across cancer types

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Abstract

Metabolic rewiring and deregulation of the cell cycle are hallmarks shared by many cancers. Concerted mutations in key tumor suppressor genes, such as *PTEN*, and oncogenes predispose cancer cells for marked utilization of resources to fuel accelerated cell proliferation and chemotherapeutic resistance. Mounting research has demonstrated that PTEN-induced putative kinase 1 (PINK1) acts as a pivotal regulator of mitochondrial homeostasis in several cancer types, a function that also extends to the regulation of tumor cell proliferative capacity. In addition, involvement of PINK1 in modulating inflammatory responses has been highlighted by recent studies, further expounding PINK1's multifunctional nature. This review discusses the oncogenic roles of PINK1 in multiple tumor cell types, with an emphasis on maintenance of mitochondrial homeostasis, while also evaluating literature suggesting a dual oncolytic mechanism based on PINK1's modulation of the Warburg effect. From a clinical standpoint, its expression may also dictate the response to genotoxic stressors commonly used to treat multiple malignancies. By detailing the evidence suggesting that PINK1 possesses distinct prognostic value in the clinical setting and reviewing the duality of PINK1 function in a context-dependent manner, we present avenues for future studies of this dynamic protein.

Key Words: apoptosis; cancer; cell cycle; inflammation; metabolic stress; mitochondral quality control; mitophagy; PINK1; tumor; Warburg effect

Introduction

PTEN-induced putative kinase 1 (PINK1) was initially identified as a downstream effector of phosphatase and tensin homolog (PTEN), a tumor suppressor frequently mutated in various human cancers (Unoki and Nakamura, 2001). As a widely expressed serine-threonine kinase with a N-terminal mitochondrial targeting motif, PINK1 has emerged as a pivotal regulator of mitochondrial homeostasis (Valente et al., 2004; Sim et al., 2006; Matsuda et al., 2013). Yet the importance of PINK1 did not gain prominence until mutations in PINK1 were implicated as a cause of autosomal recessive early-onset Parkinson's disease (PD) (Petit et al., 2005; Poole et al., 2008; Arena and Valente, 2017). Several lines of evidence indicate that PINK1 confers protection against mitochondria-dependent apoptosis induced by both intrinsic stress and environmental insults (Gautier et al., 2008; Wang et al., 2011a; Huang et al., 2016, 2017). While the role of PINK1 in neuroprotection has been well-documented, the recent rise in research on PINK1 function has led to a more comprehensive view of its anti-apoptotic mechanisms, including mitochondria quality control and cell cycle regulation (O'Flanagan et al., 2015; Leites and Morais, 2018). PINK1 pathogenicity, albeit traditionally studied in PD, has been supported in other diseases, such as cancer.

PINK1 mRNA is expressed ubiquitously across all cell types with the highest expression levels observed in the brain, heart, skeletal muscle, and testis (Unoki and Nakamura, 2001; Berthier et al., 2011). The encoded 581-amino acid protein consists of an N-terminal mitochondrial-targeting sequence, a transmembrane domain, a highly conserved kinase domain displaying homology with the Ca^{2+}/calmodulin family, and a C-terminal autoregulatory sequence (Beilina et al., 2005; Cardona et al., 2011; Kumar et al., 2017). This structural composition informs of mechanisms underlying the dual subcellular distribution of PINK1 (Lin and Kang, 2010). While endogenous PINK1 is synthesized constitutively in the cytosol as a full-length precursor (~63 kDa), the mitochondrial-targeting sequence is sufficient for mitochondrial localization. Upon import into mitochondria, PINK1 is anchored by the transmembrane domain and adopts a topology with a cytosol-facing kinase domain (Takatori and Iwatsubo, 2008; Liu et al., 2017). In the presence of mitochondria with healthy bioenergetics, the PINK1 precursor is proteolytically cleaved to produce its mature form (~52 kDa) and subsequently retranslocated to the cytosol. The preferential degradation of processed PINK1 results in a rapid turnover and low steady-state levels (Liu et al., 2017).

However, disruption of a healthy mitochondrial network abrogates its degradation and unleashes the catalytic activity of PINK1 via autophosphorylation at Ser228 and Ser402. The phosphorylation of ubiquitin and ubiquitin-like domain of Parkin at Ser65 by PINK1 has been well-characterized (Eiyama and Okamoto, 2015). Yet studies have suggested that the kinase activity of PINK1 spans to other substrates, including TRAP1 (Pridgeon et al., 2007), Mfn2 (Chen and Dorn, 2013), Miro (Wang et al., 2011), Bcl-xL (Arena et al., 2013), and HtrA2 (Plun-Favreau et al., 2007). Many of these signaling pathways converge on cell survival, lending credence to the cytoprotective function of PINK1.

While an inverse association between the prevalence of

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neurodegenerative diseases and the development of some cancers has been reported by several studies, its molecular underpinnings are yet to be fully elucidated (Driver, 2014). Contrary to the premature death of dopaminergic neurons characterizing PD, a shared phenotype among cancer cells is uncontrolled cell growth and proliferation (Devine et al., 2011). The manifold roles of PINK1 may partially explain this cross-talk, since PINK1 is commonly overexpressed in many tumor cell types but mutated in neurons affected by PD (Berthier et al., 2011). While initial epidemiological studies found an unusually low incidence of cancer in patients with PD, growing evidence has supported both an inverse and direct cancer comorbidity. PD has a lower co-occurrence with lung cancer, prostate cancer, and colorectal cancer but higher co-occurrence with melanoma, brain cancer, and breast cancer (Catalá-López et al., 2014; Ong et al., 2014). This complex relationship between neurodegeneration and carcinogenesis is corroborated by reports of shared molecular and cellular machinery that govern mitochondrial dynamics, cell cycle control, and proteostasis. Thus, this interplay raises the possibility of novel therapeutic approaches through modulating the therapeutic targets of neurodegenerative diseases in cancer and vice versa (Plun-Favreau et al., 2010). PINK1, in particular, is an attractive candidate due to the eclectic nature of this protein.

Since the discovery of PINK1 in 2001, several studies have sought to unravel the characteristics and roles of PINK1 in cancer development. Mounting data supports both an oncogenic and oncolytic mechanism of action for PINK1, demonstrating a need for future studies of this protein in the context of multiple cancers. This review will describe our current understanding of PINK1 in cancer, specifically focusing on underlying molecular signaling mechanisms while detailing its potential utility in the clinical setting.

Search Strategy and Selection Criteria

The publications selected for this review were retrieved from PubMed, Science Direct, and Google Scholar (from inception to May 10, 2020). Screening for potentially relevant literature was conducted using one or more of the following search terms: PINK1; cancer; prognosis; mitochondria; mitophagy; apoptosis; proliferation. Only articles published since 2001 were considered. The reference lists of articles compiled by this search strategy were reviewed for additional relevant articles.

PINK1 Shows Promise as a Prognostic Marker for Cancer

Due to the pro-survival effects of PINK1, recent studies have sought to decipher its potential as a prognostic factor in patients with various cancer types (Yamashita et al., 2017; Zhang et al., 2017; Chang et al., 2018). Although PINK1 expression was not significantly associated with tumor size or lymphatic invasion in ESCC patients, a correlation was reported in non-small cell lung cancer (NSCLC) patients. High PINK1 expression also predicted a poor prognosis with respect to histological differentiation and clinical stage progression in NSCLC patients (Zhang et al., 2017). When NSCLC patients were further classified into two subtypes, adenocarcinoma and squamous cell carcinoma, a significant association between high PINK1 expression and chemoresistance was observed in adenocarcinoma patients treated with adjuvant chemotherapy, but not squamous cell carcinoma patients. The differing outcomes reveal that PINK1 function may be contingent on the distinct biological characteristics of each tumor cell type (Chang et al., 2018).

While most *in vivo* studies have implicated PINK1 as a biomarker for poor survival, Agnihotri et al. (2016) noted that PINK1 negative gliomas were correlated with a worse overall survival for patients treated with temozolomide and radiation therapy. In low-grade gliomas, a decrease in PINK1 mRNA has often been observed due to the frequent deletion of chromosome 1p36, the locus of PINK1. Additionally, PINK1 mRNA was further reduced in glioblastoma and lost in all four subgroups of medulloblastoma, the most prevalent type of primary brain cancer in children (Agnihotri et al., 2016). Though there has yet to be a consensus about PINK1 *in vivo*, a better understanding of PINK1 function in multiple cancers may assist in stratifying patients for specific therapies.

PINK1 Oversees Mitochondrial Quality Control via Mitochondrial Autophagy

As a critical mitochondrial quality control mechanism, mitochondria-selective autophagy, termed mitophagy, is responsible for the clearance of dysfunctional mitochondria. Accordingly, this housekeeping function is governed by various regulators and molecular adaptors. Cells determine which signaling cascade to employ in a context-dependent fashion (Palikaras et al., 2018). For instance, basal mitophagy is PINK1-independent (McWilliams et al., 2018) and hypoxia can induce mitophagy via BNIP3, NIX, or FUNDC1 activity (Chourasia et al., 2015).

However, the loss of mitochondrial membrane potential ($\Delta\Psi_m$) results in mitophagy orchestrated by PINK1. As a prerequisite for PINK1-mediated mitophagy, $\Delta\Psi_m$ depolarization is a reliable indicator of mitochondrial impairment (Perry et al., 2011; Salimi et al., 2017; Zorova et al., 2018). Under steady-state conditions, intact $\Delta\Psi_m$ drives PINK1 import via the translocases of the outer and inner mitochondrial membrane. At the inner mitochondrial membrane, full-length PINK1 (~63 kDa) undergoes a multistep cleavage mediated by matrix processing peptidase and presenilins-associated rhomboid-like protease. The resulting 52 kDa form of PINK1 is re-exported to the cytosol, where it is degraded by the proteasome (Truban et al., 2017; Sekine and Youle, 2018). However, following $\Delta\Psi_m$ depolarization, unprocessed PINK1 accumulates and autophosphorylates at the OMM of dysfunctional mitochondria, triggering the recruitment and phosphorylation of Parkin. The concerted effort of PINK1 and Parkin then elicits a feed-forward loop due to Parkin-catalyzed conjugation of ubiquitin (Ub) to a variety of OMM proteins and subsequent phosphorylation of these Ub moieties by PINK1. Coated with p-Ub chains, the damaged mitochondria are eliminated via autophagic machinery (Kazlauskaite and Muqit, 2015; Truban et al., 2017).

While mitophagy modulation has promising implications as a therapeutic strategy, tampering with the expression of mitophagy genes, such as PINK1, generates a context-dependent, biphasic response in cancer. As a tumor-suppressive mechanism during the onset of cancer, mitophagy ensures the upkeep of functional mitochondria and maintains genomic stability (Chourasia et al., 2015; Qian et al., 2018). Mounting studies demonstrate that multiple oncogenic signaling pathways, such as KRAS, MAPK, and BCL-2, converge on mitochondria and are responsible for metabolic reprogramming (Elkholi et al., 2014; Viale et al., 2014; Nagdas and Kashatus, 2017). Therefore, there has been a renewed interest in targeting mitochondria as a selective anticancer strategy.

Maintaining mitochondrial integrity is key to cell survival, owing to the potential deleterious effects of perturbations to mitochondria quality control (Rozanov et al., 2019). Mitochondrial homeostasis is regulated by several conserved repair processes, including the selective clearance of damaged or excessive mitochondria via mitophagy. Therefore, offsetting the imbalance of mitochondrial turnover, caused by the metabolic rewiring of cancer cells, may alter their susceptibility to apoptosis (Vara-Perez et al., 2019). While preserving a basal

level of mitophagy facilitates cell survival, excessive mitophagy may foster a loss of functional mitochondria and activate apoptotic pathways (Yan and Li, 2018; Panigrahi et al., 2019). Thus, this delicate physiological balance may be the root of the intricacies of PINK1 function.

The growth of cancer stem cells, a highly tumorigenic and chemotherapy-resistant subpopulation of tumor-initiating cells, is negatively regulated by PINK1. Specifically, PINK1 phosphorylates p53, instigating a cascade that results in a reduced cancer stem cell population (Liu et al., 2017). Yet once a tumor has progressed to an advanced stage and has undergone metabolic reprogramming, mitophagy may mitigate metabolic stress, inhibiting apoptosis (Chourasia et al., 2015; Qian et al., 2018). In multidrug-resistant cancer cells, PINK1 counteracts the ramifications of impaired ΔΨm (Yao et al., 2019). By attenuating the clearance of dysfunctional mitochondria, the suppression of PINK1 expression augments the formation of reactive oxygen species (ROS) (Wang et al., 2011b; Ježek et al., 2018). The unmitigated oxidative stress further impairs mitochondrial health, sustaining a malicious self-perpetuating cycle of oxidative stress and mitochondrial damage. As a result, decreased PINK1 levels can exacerbate the apoptotic effects of toxic insults or anticancer agents, such as B5G1, a mitophagy inducer derived from betulinic acid (Ježek et al., 2018; Yao et al., 2019).

To further probe the ramifications of PINK1 loss with respect to apoptosis in NSCLC, we determined that curtailing PINK1-mediated mitophagy enhanced cytochrome c leakage into the cytoplasm, in turn activating Caspase-9. Thus, the accumulation of dysfunctional mitochondria, in conjunction with elevated levels of ROS formation, in PINK1-deficient cells made them more susceptible to apoptosis (Dai et al., 2019). As cells became more dependent on glycolysis after PINK1 knockdown, we were able to demonstrate that the NSCLC cell line A549 exhibited an increased sensitivity to the glycolytic inhibitor 3-bromopyruvate (Dai et al, 2019). Similar results were obtained when PINK1 downregulation was employed to sensitize resistant bladder cancer cells to an adenovirus carrying REIC/Dkk-3. The resulting increase in apoptosis in PINK1-downregulated cells was attributed to the enhanced generation of ROS (Berthier et al., 2011; Jin et al., 2012; Dai et al., 2019).

Further exploring the role of PINK1-dependent mitophagy on cancer cell death, Liu et al. (2018) determined that PINK1 silencing not only leads to a repression of mitophagy but also a significant reduction in $\Delta\Psi_m$, elevating the levels of mitochondrial dysfunction. Taken together, manipulation of PINK1 expression may orchestrate potent suppression of malignant tumors and render them more susceptible to anticancer agents through a mitophagy-dependent mechanism.

PINK1 Antagonizes the Warburg Effect in Tumor Cells

Garnering further support of mitophagy's role in pro- and anticancer mechanisms in established tumors, recent studies have implicated PINK1's involvement in metabolic reprogramming. Thus, PINK1-dependent mitophagy adds another layer of complexity to the Warburg effect, the propensity of cancer cells for aerobic glycolysis (Hjelmeland and Zhang, 2016; Esteban-Martínez et al., 2017). While the Warburg effect manifests differently in various cancers, cells with a Warburg phenotype tend to demonstrate an increased rate of proton production (extracellular acidification rate) and a decreased rate of oxidative phosphorylation (oxygen consumption rate) (Potter et al., 2016). This metabolic shift is a consequence of various mutations that activate oncogenes and inactivate tumor suppressor genes, as well as a hypoxic microenvironment (Cairns, 2015; Marbaniag and Lakhan, 2018). Requejo-Aguilar et al. (2014) first reported the oncogenic function of PINK1 in reprogramming glucose metabolism in mouse embryonic fibroblasts and neurons. In both cell types, loss of PINK1 prompted a ROS-mediated stabilization of hypoxia-inducible factor-1α (HIF-1α), a key driver of the Warburg effect in this cell type, and a subsequent increase in glycolytic rate. The metabolic shift to HIF-1α-enhanced glycolysis may be explained by the inherent bioenergetic needs resulting from a high proliferative status (Requejo-Aguilar et al., 2014). This finding was substantiated shortly thereafter in glioblastoma cells. Due to the elevated ROS levels associated with the loss of PINK1, inhibitory phosphorylation of FOXO3a was reduced, which then led to HIF-1α stabilization. A decrease oxygen consumption rate was also detected, further establishing PINK1 deficiency as a promoter of tumor growth and driver of the Warburg phenotype. Accordingly, PINK1 re-expression suppressed glioblastoma growth by alleviating ROS levels and attenuating HIF-1α and HIF-1α response proteins including PDK1, HK2, LDHA and VEGFA (Agnihotri et al., 2016).

To further probe the mechanism of action of PINK1 in metabolic reprogramming, Li et al. (2018) focused on the contribution of mitochondrial iron to the acceleration of pancreatic tumorigenesis. It was concluded that PINK1 deficiency led to excessive mitochondrial iron accumulation, in turn heightening ROS production and bolstering a Warburg phenotype, including higher lactate levels, increased extracellular acidification rate, and decreased oxygen consumption rate (Li et al., 2018; Kang et al., 2019). Pre-treatment with deferiprone, a mitochondrial iron chelator, corrected for this metabolic abnormality, which lends credibility to the significance of mitochondrial iron overload in exacerbating the Warburg effect (Li et al., 2018).

The metabolic response to PINK1 loss, however, is context-dependent and inconsistent among cell types (Agnihotri et al., 2016). Agnihotri et al. (2016) cited an incomplete suppression of PINK1 and subsequent maintenance of ROS levels below the anti-growth threshold as a possible determinant. Interestingly, the outcome of HIF-1α stabilization differs between mitophagy-deficient and mitophagy-proficient tumors, suggesting that the duality may be contingent on the status of PINK1 expression (Li et al., 2018). The dependency of HIF1α stabilization on ROS provides further grounds for this link between PINK1 and metabolic reprogramming (Aguilar et al., 2004).

This accumulating evidence regarding PINK1's involvement in the Warburg effect may also be grounded in the structural basis for this mitochondrial respiratory injury. Kiebish et al. (2008) proposed that abnormalities in cardiolipin (CL), a signature phospholipid that predominantly exists in the inner mitochondrial membrane, contribute to the Warburg phenotype and were correlated with impaired electron transport chain efficiency. Mutations in PINK1 have been reported to decrease CL production due to increased mitochondrial ROS levels. This accumulation of mitochondrial stress could be a consequence of complex I defects (Vos et al., 2017). In PINK1 mutants, the ubiquinone reductase ability of complex I is hindered due to a loss of phosphorylation of complex I subunit NdfA10 at Ser250. Consequently, electron transport between complex I and ubiquinone is inefficient, reducing the ability of tumors to procure energy from sources other than glucose (Morais et al., 2014; Vos et al., 2017). These findings suggest that CL abnormalities related to PINK1 mutations may underlie the respiratory injury characteristic of the Warburg phenotype. Taken together, the involvement of PINK1 on CL production and electron transport chain activity, in conjunction with the mechanisms governing the metabolic switch, strengthens the supposition of PINK1 as a negative regulator of the Warburg effect.

PINK1 Bridges Mitochondrial Dynamics with Cell Cycle Progression

While the immediate consequences of altering PINK1 expression primarily convene in the mitochondria, the downstream effects of PINK1-dependent metabolic rewiring extend to other cell survival mechanisms, including the regulation of cell division, across various cell types (Mishra and Chan, 2014). For example, cell cycle progression parallels remodeling of mitochondrial morphology via fission-fusion machinery (Salazar-Roa and Malumbres, 2017). Fission, in particular, is a prerequisite for mitochondria to be equally partitioned among daughter cells during mitosis (Mishra and Chan, 2014). PINK1 has been implicated in maintaining the balance between fission and fusion, with PINK1-deficient cells defaulting to a fission phenotype (Rojas-Charry et al., 2014; Li et al., 2017). Li et al. (2017) has noted excessive mitochondrial fragmentation and ensuing heightened apoptosis in PINK1-deficient breast cancer cells. Further investigation revealed that PINK1 knockdown resulted in elevated activity of dynamin-related protein 1 (Drp1), a GTPase that promotes mitochondrial fission when recruited to the outer mitochondrial membrane and phosphorylated (Mishra and Chan, 2014; Li et al., 2017). Accordingly, PINK1-deficient cells demonstrated a greater degree of Drp1 localization in the mitochondria (O'Flanagan et al., 2015). Conversely, it was noted that Drp1 deficiency rescues the wild-type phenotype in neuronal cells, further corroborating PINK1's role in regulating the phosphorylation status of Drp1 (Lutz et al., 2009). Despite interfering with the Drp1 phosphorylation, loss of PINK1 also resulted in sustained phosphorylation of Drp1 at Ser585, which suggests a protracted pre-cytokinesis phase.

Although prior studies have elucidated the involvement of PINK1 in maintaining fission-fusion balance, O'Flanagan et al. (2015) first reported PINK1-mediated fission in the context of proper cell cycle progression. PINK1-deficient mouse embryonic fibroblast cells could be differentiated from their wild-type counterpart due to their morphological differences. A flattened and enlarged shape and higher frequency of multinucleation, which are typical hallmarks of senescent cells, were characteristic of the PINK1-null phenotype.

Subsequent analysis of the cell cycle profile unveiled the underlying molecular basis for this alteration: increased arrest at G_2/M (cytokinesis) and decreased arrest at G_0/G_1 (cell cycle exit) (O'Flanagan et al., 2015; Liu et al., 2018; Sarraf et al., 2019). Thus, PINK1 silencing interfered with cell cycle progression, consequently restraining cancer cell proliferation (O'Flanagan et al., 2015; Liu et al., 2018). This transformed phenotype was reverted by PINK1 overexpression, implicating PINK1 as a regulator of the cell cycle (O'Flanagan et al., 2015). In accordance with these findings, inhibition of mitotic spindle formation using nocodazole and release from this block resulted in a decrease of wild-type PINK1 cells in the G_2/M phase but not PINK1-deficient cells. Since chromosome segregation and nuclear envelope reformation were still observed in PINK1-deficient cells, the irregularity was attributed to cytokinesis (O'Flanagan et al., 2015).

More in-depth characterization of the interactions between PINK1 and various cell cycle proteins has substantiated the interplay between metabolic and cell division pathways. For example, PINK1 has been shown to phosphorylate Bcl-xL (Ser62), an anti-apoptotic protein relevant in both mitochondrial energetics and cell cycle arrest (Arena et al., 2013; Bah et al., 2014). In addition to inhibiting mitochondrial outer membrane permeabilization by binding pro-apoptotic Bax, Bcl-xL heightens mitochondrial energy capacity by localizing to the inner mitochondrial membrane where it modulates the F1F0 ATP synthase (Chen et al., 2011). However, phosphorylation of Bcl-xL (Ser62) decreases its affinity for Bax, allowing for pore formation. While the functional role of phosphorylated Bcl-xL is still a matter of debate, Wang et al. (2012) has reported that phospho-Bcl-xL (Ser62) interacts with Cdk1 to stabilize G_2 arrest. Thus, PINK1 may regulate a pro-apoptotic response via Bcl-xL, although further investigation of the effect of PINK1 on the multifunctional Bcl-xL will grant a more nuanced understanding. Consistent with this finding, fibroblasts lacking PINK1 demonstrated a shortened G_0/G_1 phase, as well as lengthened S and G_2/M phases, which were attributed to HIF1α stabilization by PINK1 (Requejo-Aguilar et al., 2014).

Despite total histone H3 levels not differing significantly between PINK1-deficient and wild-type cells, a delay in phosphorylation was noted in PINK1-deficient cells, which alludes to a slower rate of mitosis (O'Flanagan et al., 2015). In addition, Sarraf et al. (2019) identified genetic interplay with cyclin-dependent kinase 1 (Cdk1) and cyclin-dependent kinase 2 (Cdk2), which regulate G_1/S and G_2/M transitions respectively. They noted that knockdown of Cdk1 and Cdk2 counteracted the cell cycle alterations due to PINK1 loss (Sarraf et al., 2019). Further investigation of this relationship for G_1/S transition revealed attenuated levels of cyclin D1, a CDK regulator and prerequisite for cell cycle entry, in PINK1-deficient cells (O'Flanagan et al., 2015). In a similar light, Zhang et al. (2017), found upregulation of cyclin D1 and downregulation of p27, a CDK inhibitor to be a result of PINK1 overexpression. Taken together, PINK1's function in maintaining mitochondrial homeostasis translates to a crucial role in maintaining accelerated cell cycle progression in multiple tumor types.

PINK1 Exerts its Pro-Survival Effects Beyond Mitochondria

Although the contribution of PINK1 to preserving mitochondrial homeostasis has been widely documented, this multifaceted protein confers cellular protection at the crossroad of mitochondrial and cytosolic pathways. The lesser-known cytosolic pool of PINK1 has been implicated in signaling cascades critical to cell growth and survival, including the PI3-kinase (PI3K)/Akt, valosin-containing protein (VCP), and protein kinase A (PKA) pathways. Considering that PINK1 was named for its induction by PTEN, which is a primary inhibitor of the PI3K/Akt pathway (Georgescu, 2010), PINK1 has been a candidate regulator of PI3K/Akt signaling since its discovery. While both insulin and insulin-like growth factor-1 exert neuroprotection by activating the Akt pathway, the absence of PINK1 was found to impair Akt phosphorylation. This finding suggests that PINK1 expression is necessary for insulin-like growth factor-1 and insulin to mediate Akt cell survival signaling and PINK1-deficient neurons have a lower threshold for stress-induced apoptosis (Akundi et al., 2012). Since insulin-like growth factor-1 suppresses the tumor suppressive activity of PTEN and activates the PI3K/Akt pathway in cancer (Ma et al., 2010), a lack of PINK1 may also render cancer cells more vulnerable to apoptosis.

Seeking to elucidate the mechanisms by which PINK1 activates Akt signaling, Furlong et al. (2019) studied interactions between PINK1 and Akt in the absence of growth factors. PINK1 was reported to phosphorylate PI3-K p85 and promote the accumulation of its product PIP3 at the plasma membrane, which is a prerequisite for Akt signaling. The constitutive activation of Akt by PINK1, which was independent of growth factors, implicate that PINK1 may coordinate a short-term protective response to assure cell survival until growth factors are available (Furlong et al., 2019). As Akt is becoming an increasingly attractive target in anticancer therapy, these mechanistic insights regarding PINK1 could provide therapeutic implications.

Wang et al. (2018) further expounded the diverse abilities of cytosolic PINK1, particularly delineating a novel PINK1-VCP-PKA-P47 signaling cassette. By serving as a PKA kinase, PINK1 upregulates the phosphorylation of VCP co-factor p47. Since PINK1 also binds the VCP-p47 complex, it was implicated as an intermediary between PKA and VCP-p47 (Wang et al., 2018). This finding poses the possibility of targeting PINK1 to modulate the downstream VCP and PKA signaling pathways in cancer. Previous studies have determined the involvement of VCP and PKA in cell growth and survival independently across various cancer types, highlighting the potential of inhibitors to elicit antitumor activity (Magnahi et al., 2013; Sapio et al., 2014; Parzych et al., 2019). Thus, this warrants further investigation to substantiate the role of PINK1 in a spectrum of cancer signaling cascades, including PI3K/Akt, VCP, and PKA. Continued study of PINK1 beyond its mitochondrial functions may potentially reveal insights for novel therapeutic approaches.

PINK1 Modulates Inflammatory Responses

The first reliable cancer treatments primarily consisted of drugs that damaged the DNA of rapidly dividing cells. More recently, a greater emphasis has been placed on studying the immune system with respect to cancer progression, especially since the anti-cancer potential of the immune system has now been unleashed with checkpoint inhibitors, such as pembrolizumab (Nghiem et al., 2016) and nivolumab (Motzer et al., 2015).

PINK1 and Parkin are expressed in myeloid cell lineages (Li et al., 2019; Zhou et al., 2019) and modulate inflammatory responses in a context-dependent manner. For example, PINK1 was shown to mediate the macrophage pro-inflammatory response to vesicular stomatitis virus. PINK1 downregulation reduced the levels of interferon-B and interleukin (IL)-6 produced in response to viral infection. Interestingly, infection with vesicular stomatitis virus, respiratory syncytial virus, or herpes simplex virus downregulated PINK1 mRNA in primary macrophages (Zhou et al., 2019). These results illustrate that PINK1 may be key to mounting a successful antiviral defense and that viruses can overcome host immune defenses by targeting PINK1. However, Parkin has been shown to mitigate antiviral immunity by reducing mitochondrial ROS production in response to viral infection. Mitochondrial ROS induction induces NLR family, pyrin domain containing 3 inflammasome activation, which in turn leads to the production of inflammatory cytokines, such as IL-1B, IL-6, chemokine (C-X-C motif) ligand 1, and C-C motif chemokine ligand 2 (Li et al., 2019). These findings suggest that while PINK1 and Parkin seem to possess a concerted function in tumor progression, these proteins may exert opposing effects in the setting of inflammation and their functions are likely context-dependent.

Findings by Sliter et al. (2018) contribute to the complexity of the relationship between PINK1/Parkin and inflammatory responses. In particular, they elucidated that mitochondrial stress leads to the release of damage-associated molecular patterns that can induce an innate immune response. Their model, which utilized exhaustive exercise, demonstrated that Parkin- or PINK1-null mice exhibit a strong inflammatory response, underpinned by increased serum IL-6 and interferon-B1 (Sliter et al., 2018). STING deletion was able to ablate the pro-inflammatory phenotype and mitigate pro-inflammatory cytokine production. Further investigation in the clinical context revealed that patients with mono- or bi-allelic Parkin mutations display elevated cytokines (Sliter et al., 2018). These findings suggest that PINK1 and Parkin may exert functions specific to sterile inflammation and inflammatory conditions induced by viral infection.

Further supporting PINK1 as a repressor of the innate immune response, Sun et al. (2018) determined that the loss of PINK1 elicited the abnormal expression of microglial IL-10 and astroglial transforming growth factor-β expression. Due to the resulting augmentation of glia-mediated neuroinflammation, co-cultured neurons were more vulnerable to apoptosis (Sun et al., 2018). Thus, the protective function of PINK1 against neuronal loss may be imputed, in part, to its involvement in the inflammatory response. Yet the role of PINK1 in inflammation spans beyond innate immune responses. By inhibiting the formation of mitochondria-derived vesicles and subsequently hindering the presentation of mitochondrial antigens, PINK1 has been suggested to suppress the adaptive immune response (Matheoud et al., 2016). Interestingly, after intestinal infection with Gram-negative bacteria (LPS^+), PINK1-null mice exhibited an increased infiltration of cytotoxic $CD8^+$ T cells in the brain (Matheoud et al., 2019). Beyond potential implications for neuronal loss, $CD8^+$ T cells can expose tumor cells to T cell attack. Several studies have implicated $CD8^+$ T cells as a mediator of the anti-tumor activity in the tumor microenvironment of various cancer types (Piersma et al., 2007; Kim and Ahmed, 2010; Kmiecik et al., 2013). Thus, the involvement of PINK1 in elevating $CD8^+$ T cell levels could translate into a positive prognosis for cancer patients.

With respect to myeloid cells, there now exists data that shows tumors, such as glioblastoma, are heavily comprised of macrophages and microglia, innate immune cells of the CNS (Graeber et al., 2002). Macrophages and microglia can assist tumor cell survival, promote neoangiogenesis, and impede the actions of cytotoxic lymphocytes by promoting an immunesuppressive tumor microenvironment (Miyauchi et al., 2018). Consequently, it will be important to delineate how PINK1 and Parkin modulate the oncogenic or oncolytic potential of these cells to gain further insight into how these proteins affect clinical outcomes.

Concluding Remarks

Since the discovery of PINK1 two decades ago, accruing evidence has cast light on its eclectic nature. PINK1 has been reported to be ubiquitously expressed in various cell types across a spectrum of diseases ranging from neurodegenerative diseases to cancer. This review communicates the findings from a comprehensive body of current literature regarding PINK1's function beyond ameliorating impaired mitochondrial integrity in PD. PINK1 acts at the crossroads of various pathways critical for cell survival and cell death balance: mitochondria quality control, mitochondrial bioenergetics, and cell cycle regulation. This complex interplay of genetic and protein interactions underlines the duality of PINK1 in promoting pro- and anti-tumorigenic properties (**Table 1**). While PINK1's protective role promotes cell survival, excessive activation of these stress-alleviating mechanisms orchestrates the induction of apoptosis. Future research should aim to further elucidate how modulating PINK1 expression manifests in specific cancer cell biologies and perturbs disease progression. Considering its well-characterized role in neurodegeneration, a more nuanced perspective of PINK1 in gliomas, in particular, could provide therapeutic value and be fruitful in abating invasion into neighboring non-malignant tissue. In addition, PINK1's involvement in the inflammatory response necessitates further investigation of PINK1 function in immune cells that functionally interact with tumor cells. With a better understanding of its context-dependent response, PINK1 could provide a promising therapeutic target for a range of diseases.

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Table 1 | **Role of PINK1 expression in different cancers**

Cancer	Effect *in vitro*	Effect *in vivo*	Reference
Bladder cancer	↓ Apoptosis	NT	Jin et al. (2012)
Breast cancer	↓ Apoptosis	NT	Berthier et al. (2011)
Breast cancer	↑ Cell proliferation	NT	O'Flanagan et al. (2015)
Cervical cancer	↑ Cell proliferation	NT	O'Flanagan et al. (2015)
Esophageal cancer	↑ Chemoresistance	↑ Chemoresistance	Yamashita et al. (2017)
Glioblastoma	↓ Cell proliferation	↓ Tumor growth	Agnihotri et al. (2016)
Hepatic cancer	↑ Cell proliferation	NT	Liu et al. (2017)
Hepatic cancer	↓ Apoptosis	NT	Yao et al. (2019)
Non-small cell lung cancer	↑ Cell proliferation ↓ Apoptosis	NT	Dai et al. (2019)
Non-small cell lung cancer	↑ Cell proliferation ↓ Apoptosis	↑ Tumor growth	Zhang et al. (2017)
Non-small cell lung cancer	↑ Cell proliferation ↓ Apoptosis	↑ Tumor growth	Liu et al. (2018)
Non-small cell lung cancer	NT	↑ Chemoresistance	Chang et al. (2018)
Pancreatic cancer	↑ Apoptosis	↓ Tumor growth	Li et al. (2018)

NT: Not tested; ↑: increase; ↓: decrease.

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