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Functions and characteristics of PINK1 and Parkin in cancer

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1. ABSTRACT

Most of the Parkinson disease (PD) linked genes are also associated with cancers. In particular, phosphatase and tensin homologue-induced kinase 1 (PINK1) and Parkin, both of which are involved in recessively inherited familial forms of PD linked to mitochondrial dysfunction, appear to be abnormally expressed in cancers. Functional studies have revealed that PINK1 recruits Parkin to mitochondria to initiate mitophagy, an important autophagic quality control mechanism that rids the cell of damaged mitochondria. Although PD and cancer are obviously disparate human disorders, there is an evidence for low cancer rates in patients with PD. The relationship between cancer rates and PD might be related to the involvement of common pathways in both diseases. This paper provides a concise overview on the cellular functions of the PINK1 and Parkin.

2. INTRODUCTION

Most of the Parkinson disease (PD) linked genes are also associated with cancers. In addition, there are evidences for low cancer rates in patients with PD (1). This might be related to the involvement of common genes in both diseases (1). For example, PINK1 and Parkin, both of which are involved in familial forms of PD, appear to be abnormally expressed in cancers (2, 3). Inhibition of PINK1 results in an elevation of reactive oxygen species and the accumulation of mitochondrial oxidative lesions. PINK1 has been shown to protect against cell death induced by proteasome inhibition and oxidative damage (4, 5). The oxidative stress is caused by an imbalance between the production of ROS and the ability of cells to neutralize their reactive intermediates. PINK1and Parkin may play a pivotal role in a common mitochondrial homeostasis. Mitochondria have been recognized as an essential organelle in the establishment of tumor characteristics, proliferative capacity, and adaptation to cellular environment. Interestingly, Parkin, which encodes an ubiquitin ligase, plays a role in cancer as a putative tumor suppressor (6, 7). Mutations in Parkin gene were originally identified as a genetic contributor of PD, however, they had also been reported in several types of cancer. In addition, Parkin gene is frequently targeted by deletion and inactivation in human malignant tumors (8). It is now clear that Parkin gene alterations are not restricted to familial forms of PD but also occur frequently in a wide variety of malignancies which include glioblastoma and lung cancer (9). Parkinson disease and cancer are obviously disparate human disorders. The relationship between cancer rates and PD might be related to the involvement of common pathways in both diseases. The overlapping of genes involved in PD and cancer would also imply a shared pathogenic pathway. Unraveling the link between PD and cancer may open a therapeutic window for both diseases. Therefore, PINK1 and Parkin represent a potential

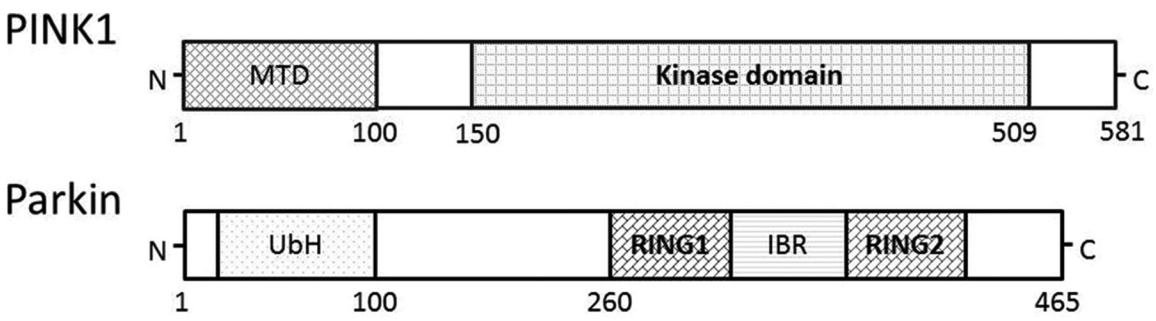

Figure 1. Schematic illustration indicating the domain structures of PINK1 (upper) and Parkin (lower) proteins. The consensual important domain structures for each protein are depicted. MTD= mitochondrial targeting domain, UbH= Ubiquitin homology domain, RING1, RING2= RING finger domain, IBR= In Between Ring fingers

therapeutic target for the treatment of cancers. However, the mechanism underlying the differing cellular fates of each disease remains unclear.

3. EXPRESSION AND CHARACTERISTICS OF PINK1 AND PARKIN

PINK1(phosphatase and tensin homolog (PTEN)-induced kinase 1) mRNA is expressed ubiquitously (10), which encodes a 581 amino acid putative mitochondrial serine/threonine kinase **(**Figure 1). An N-terminal mitochondrial-targeting signal domain is sufficient for mitochondrial INTRODUCTION of PINK1 (11). PINK1 is then predominantly found in the mitochondrial inner membrane and inter-membrane space, although a fraction of PINK1 exists in the mitochondrial outer membrane with the kinase domain facing the cytosol (12). PINK1 can be processed into at least two shorter forms, which are distributed in both mitochondrial and cytosolic compartments. The cytoplasmic localization of PINK1 may be affected by N-terminal cleavage. The cytoplasmic PINK1 is quickly degraded by proteasome (13). Adding to the variety of cell-survival functions of PINK1, it has been shown to phosphorylate the mitochondrial heat shock protein 75 (Hsp75), also known as tumor necrosis factor receptor-associated protein 1 (TRAP1). The TRAP1 is increasing for neuronal survival against oxidative stress or heat shock by preventing the release of cytochrome-c from mitochondria (14). Consequently, PINK1 protects cells from apoptosis in response to oxidative stress such as H_2O_2 and suppresses cytochrome-c release. The TRAP1 may be a direct substrate for PINK1, which localize primarily in the mitochondrial matrix and at extra-mitochondrial sites. The mitochondrial serine protease HtrA2 has also been identified to be regulated by PINK1 (15). The HtrA2 is phosphorylated and physically interacts with PINK1 in relation to a signaling pathway (15). HtrA2 is released from the inter-membrane space of mitochondria during apoptosis to the cytosol (16). Deletion of HtrA2 gene causes mitochondrial dysfunction leading to a neurodegenerative disorder like PD (15). Whether HtrA2 is a direct PINK1 substrate is unclear, and it is possible that differences in cell viability resulting from PINK1 inactivation may affect HtrA2 through other kinase such as p38 MAPK or JNK. PINK1 may also interact with Beclin1. Full-length PINK1 interacts with the Beclin1 (17), a key pro-autophagic protein implicated in the pathogenesis of Alzheimer's and Huntington's diseases, which enhance starvation-induced autophagy. Overexpression of PINK1 protects neuronal cells against various stresses, while down-regulation of PINK1 sensitizes the cells to various stresses. PINK1 enhances phosphorylation of AKT at Ser-473, and the AKT phosphorylation may be due to activation of mammalian target of rapamycin complex 2 (mTORC2) by PINK1 (18).

Mutations in the Parkin gene (*PARK2*) are originally identified as a genetic contributor of autosomal recessive PD (19). The Parkin gene is located on chromosome 6q25.2.-6q27 (19, 20). The gene product Parkin is a 52 kDa protein with an N-terminal ubiquitin-like (Ubl) domain followed by a 60 amino acids linker and four zinc-finger domains (19). Parkin protein is an E2-dependent E3 ubiquitin ligase that binds UbcH7 and UbcH8 (19, 21). The E3 ubiquitin ligase is an enzyme that catalyzes the transfer of ubiquitin, a small 76 amino acids protein, from an E2 ubiquitin-conjugating enzyme to a protein substrate. The last three zinc-finger

domains form an RING1 and RING2 (RBR) module (Figure 1), which is also found in many other E3 ubiquitin ligases (21). Parkin has been implicated in various cellular processes for which many substrates have been suggested (22, 23). Importantly, Parkin is recruited to depolarized mitochondria where it plays a role in the clearance of proteins damaged as a result of oxidation by autophagy (mitophagy) (24), as well as in the metabolism of dopamine (25). Parkin controls dopamine utilization in midbrain dopaminergic neurons (25). Regulation of Parkin is through post- translational modifications. In particular, phosphorylation plays a key role. PINK1 kinase activity is required for the recruitment of Parkin to depolarized mitochondria and for the activation of its ubiquitin-ligase activity (26). PINK1 phosphorylates Ser65 in the Ubl domain of Parkin, which increases its ubiquitin ligase activity (27). So, PINK1 and Parkin are in close proximity on depolarized mitochondria (28, 29). Parkin levels may be regulated by auto-ubiquitination, and its coupling to the de-ubiquitinating enzyme may regulate its stability in cells (30, 31).

4. PINK1 AND PARKIN INVOLVED IN MITOCHONDRIAL HEALTH

Mitochondria play an important role in cellular metabolic processes by serving as generators of ATP and apoptotic signaling pathways. Cells rearrange their mitochondrial populations according to local ATP needs. Molecular genetics has linked mitochondrial dysfunction to the pathogenesis of PD and cancers by the discovery of several inherited mutations in the gene products that associate with mitochondria (32). Prolonged ROS exposure can cause mitochondrial dysfunction, because proteins involved in oxidative phosphorylation and the electron transport chain are sensitive to the oxidative stress (33, 34). PINK1 has been reported to protect against oxidative stress by phosphorylating a mitochondrial chaperone TRAP1/ Hsp75 (14). PINK1 co-localizes and interacts with the TRAP1 in the mitochondrial intermembrane space. Upon phosphorylation, the TRAP1 prevents cytochrome c release. In the absence of TRAP1, over-expression of wild type PINK1 is unable to protect cells against oxidative stress mediated apoptosis, indicating that TRAP1 is essential downstream target for the pro-survival effects of PINK1 (14). The ability of PINK1 to phosphorylate TRAP1 is also impaired by kinase inactivating mutations of PINK1. PINK1 dependent phosphorylation of HtrA2 enhances its protease activity leading to enhanced survival against oxidative stress (15, 35). An interaction of PINK1 with HtrA2 indicating the possibility of common prosurvival pathway has been shown in drosophila models (36). However, the HtrA2 is not essential for all the protective functions of PINK1 in Drosophila (36, 37). Another mitochondrial protease rhomboid-7 has been implicated in post-translational regulation of both PINK1 and HtrA2 (38, 39). A rhomboid-like serine protease, PARL, can affect the proteolytic processing of the PINK1 (40). Normal PINK1 localization and stability requires catalytic activity of the PARL. The PARL cleaves human PINK1 within its conserved membrane anchor (41). Upon depolarization of the mitochondrial membrane, the import of PINK1 and PARL-catalyzed processing is blocked, leading to accumulation of the PINK1 precursor (41). PARL-catalyzed removal of the PINK1 signal sequence in the import pathway acts as a cellular checkpoint for mitochondrial integrity. Interestingly, PD-causing mutations decrease the processing of PINK1 by PARL (42). PARL may mediate differential cleavage of PINK1 depending on the health status of mitochondria.

The neuroprotective activities of PINK1 depend on its mitochondrial localization. A protein kinase MARK2 phosphorylates and activates the PINK1 (43). Mutation of the Thr-313 in PINK1 shows toxic effects with abnormal mitochondrial distribution in neurons. Both MARK2 and PINK1 have been found to colocalize with mitochondria and regulate their transport. So, MARK2 may be an upstream regulator of PINK1 and regulate the mitochondrial trafficking. Mature PINK1 is free to be released into the cytosol or the mitochondrial inter membrane space. Targeting of this precursor to the outer mitochondrial membrane has been shown to trigger the mitophagy (44) **(**Figure 2). PINK1 silencing also results in mitochondrial respiratory dysfunction. Cells lacking PINK1 function have increased basal cytoplasmic and mitochondrial ROS production (45). It has been shown that PINK1 knockout mice exhibit impaired mitochondrial respiration and decreased activity of oxidative phosphorylation (46). Loss of PINK1 leads to severe alterations in mitochondrial homeostasis by the increased mitochondrial ROS inducing an increase in mitophagy (47). In addition, the impaired mitochondrial respiration can be worsened by exposure of the mitochondria to heat shock (46). Thus, PINK1 has a pivotal role in mitochondrial quality control via the mitochondrial stabilization, phosphorylation of chaperones. Failure of mitochondrial quality control eventually contributes to the cell death.

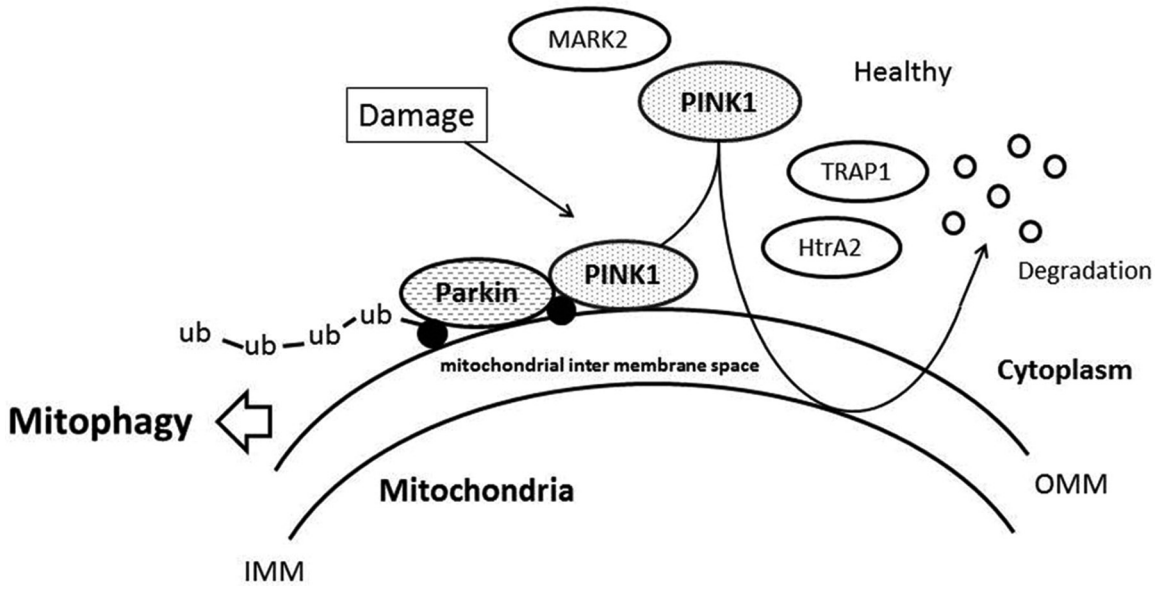

Figure 2. A hypothetical schematic representation and overview of PINK1 and Parkin regulatory pathway for mitophagy. Under healthy state, PINK1 is degraded within mitochondria. This may be inhibited by mitochondrial damage, resulting in PINK1 and Parkin accumulation in the outer membrane of mitochondria. Parkin is supposed to ubiquitinate unidentified substrate (black circle), resulting in the induction of the mitophagy. Note that some critical pathways have been omitted for clarity. OMM: outer mitochondrial membrane; IMM: inner mitochondrial membrane

PARL deficiency impairs Parkin recruitment to mitochondria, suggesting PINK1 processing and localization is essential in determining its interaction with Parkin (48). With mitochondrial damage, PINK1 facilitates aggregation of depolarized mitochondria. When mitochondrial import is compromised by depolarization, PINK1 accumulates on the mitochondrial surface where it recruits Parkin from the cytosol, which in turn mediates the mitophagic destruction of mitochondria in order to initiate mitophagy, an autophagic control mechanism that clears damaged mitochondria. Transient overexpression of Parkin further augments mitochondrial autophagy even in PINK1 deficient cells resulting in cytoprotection (49). Parkin can be phosphorylated by PINK1 in its RING finger domain, which may promote translocation of Parkin to mitochondria (50). In healthy mitochondria, PINK1 is rapidly degraded in a process involving both mitochondrial proteases and the proteasome. Parkin expression is clearly reduced in the absence of PINK1, and loss of Parkin function is sufficient to induce the abnormal mitochondrial morphology. Therefore, the importance is reflected by the neuroprotective properties of Parkin in counteracting oxidative stress and improvement of mitochondrial functioning. Moreover, activation of Parkin upon mitochondrial membrane depolarization induces its degradation through the proteasome, suggesting that the auto-inhibition of Parkin may protect itself from ubiquitin-mediated degradation (51).

5. PINK1 AND PARKIN IN CANCER

Mitochondrial dysfunction has been implicated in numerous human conditions including cancer (52). Mitochondria go through a series of morphological and functional alterations during the carcinogenesis. Cellular transformation is a multistep process that may require an undetermined sequence of genetic alterations and changes in intracellular signaling (53). The metabolic profile in transformed cells is altered to accommodate their proliferation, confer resistance to cell death, or facilitate metastasis. The mechanisms of the transformation may provide targets for anticancer treatment at several levels. Interestingly, many alkaloids exert their anticancer activities affecting some functions of the cancer-mitochondria via inducing mitochondria-dependent apoptosis and autophagy and inhibiting mitochondrial metabolic pathways (54, 55). ROS generate DNA damage of which pathological consequence including cancer is well established. In addition to the notion that

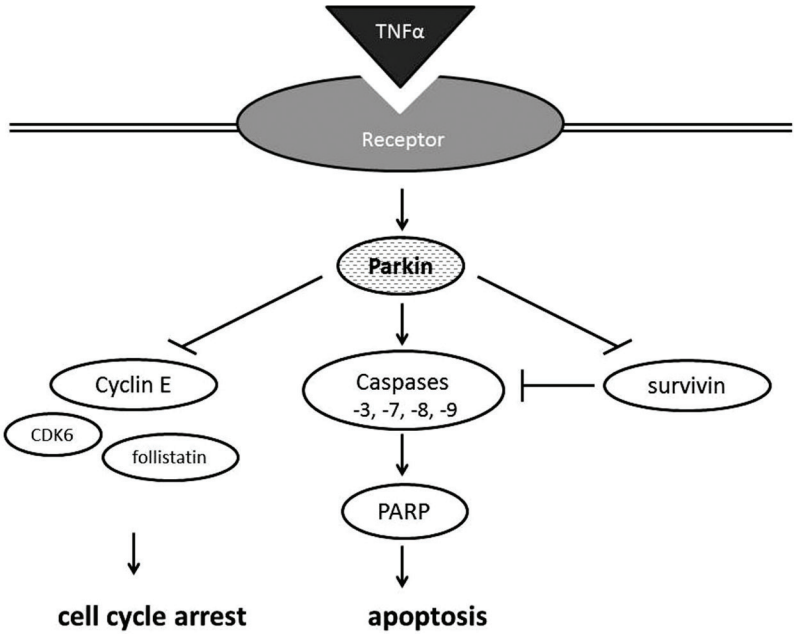

Figure 3. Implication of Parkin for cell cycle arrest and apoptosis. A schematic model showing putative points of parkin involvement is shown. Note that some critical molecules have been omitted for clarity.

oxidative DNA damage causes transformation of cells, recent studies have revealed that mitochondrial deficiencies alter the cell growth after the cell transformation (56, 57).

PINK1 has been shown to be down-regulated in the absence of PTEN (58). Inhibition of the PI3K/AKT pathway and the up-regulation of PINK1 by PTEN suggest the involvement of PINK1 in both cancer and PD. The PTEN gene is a tumor suppressor gene encoding a multifunctional phosphatase, which plays an important role in inhibiting the PI3K/AKT pathway and mutations in PTEN have been found in many human cancers. Consistently, PINK1 has been identified as an essential element for survival and important as a potential cancer drug target (59). Therefore, PINK1 appears to be a novel candidate as a mediator of the PTEN growth-suppressive signaling pathway. In contrast, decreases in Parkin expression have an essential role in tumorigenesis suggesting that Parkin is a putative tumor suppressor. In a variety of cancers, alternative transcripts were found due to gene deletion and duplication in Parkin gene (60). Abnormal methylation in *Parkin* gene results in a decreased expression of Parkin. Overexpression of Parkin represses cell growth, which results in the degradation of ubiquitin-mediated cyclin E and subsequent cell cycle arrest (Figure 3). Accumulation of the Cyclin E, a cell-cycle related G1 cyclin whose accumulation is associated with cancer development, is therefore associated with Parkin deficiency in several proliferative cancer cell lines (61). Parkin functions as an E3 ubiquitin ligase associated with the ubiquitin-proteasome system, and one of its substrates is cyclin E (61). Simultaneous mutation in both Parkin and *APC* genes accelerates colorectal carcinogenesis (62). Curiously, the Parkin exhibits an E3-independent function in the control of gene transcription. Among the genes regulated by the Parkin is TP53, a well-established tumor suppressor, whose expression is repressed by functional Parkin (63). Other genes whose expression is also regulated by Parkin are cyclin-dependent kinase 6 (CDK6) and follistatin, whose expression is thought to promote carcinogenesis. Parkin reduces cell growth by inducing expression of CDK6 (64). Ectopic parkin expression in parkin-deficient breast cancer cells mitigates their proliferation rate (64). In breast cancer, Parkin stabilizes microtubules and increases susceptibility to anti-cancer agents. Parkin expression also repairs susceptibility to TNFα-induced cell death. This process is mediated by decreased expression of survivin and the activation of caspase -3, -7, -8, -9, and PARP (65)

(Figure 3). Restoration of Parkin expression in the Parkin-deficient HeLa cell line restored susceptibility to TNFα-induced cell death. It has been reported that Parkin dysfunction is relevant to glioma-development and that restoration of functional Parkin expression in glioma cells reduces their growth via a mechanism that involves Parkin-mediated down-regulation of the cyclin E and the AKT signaling (8). Restoration of Parkin expression in Parkin-deficient cancer cells results in a marked decrease in their proliferation rate. Furthermore, Parkin-null mice exhibit a tendency to develop cancer (8). The Parkin pathway activation is predictive of survival prognosis of their patients (8). Accordingly, Parkin may function as a tumor suppressor.

6. PERSPECTIVE

PINK1 is a mitochondrial kinase that promotes cell survival, particularly under conditions of oxidative stress. Although the precise physiological substrate of PINK1 is not fully resolved, it is clear that the kinase activity is important for the function in the mitochondrial quality control monitoring degradation of damaged mitochondrial proteins. The mechanisms by which wild type PINK1 and Parkin promote interconnected mitochondrial networks may involve different steps in mitochondrial quality control. The involvement of PINK1 and Parkin in mitochondrial dysfunction has been intensively investigated in cancer. PINK1 and Parkin seem to exert different effects in different types of cancers, and therefore, the mechanisms by which PINK1 and Parkin suppress tumorigenesis diverge. Further studies are needed to determine the exact mechanisms by which PINK1 and Parkin function in carcinogenesis to understand the precise mitochondrial protective roles of PINK1 and Parkin in terms of their relationship to each other for roles in carcinogenesis.

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Abbreviations: Hsp75: heat shock protein 75, HtrA2: high temperature requirement protein A2, JNK: c-jun N-terminal kinase, p38 MAPK: p38 mitogen-activated protein kinase, MARK2: Microtubule affinity-regulating kinase 2, mTORC2: mammalian target of rapamycin complex 2, PARL: presenilin-associated rhomboid-like, PD: Parkinson disease, PINK1: PTEN-induced kinase-1, phosphatase and tensin homologue-induced kinase 1, PTEN: phosphatase and tensin homolog, TRAP1: tumor necrosis factor receptor-associated protein-1, Ubl: ubiquitin-like

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