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REVIEW

An emerging role of PARK2 in cancer

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Abstract *PARK2* (*PARKIN*) is an E3 ubiquitin ligase involved in multiple signaling pathways and cellular processes. Activity of PARK2 is tightly regulated through inter- and intra-molecular interactions. Dysfunction of PARK2 is associated with the progression of parkinsonism. Notably, frequent PARK2 inactivation has been identified in various human cancers. *Park2*-deficient mice are more susceptible to tumorigenesis, indicating its crucial role as a tumor suppressor. However, biological studies also show that PARK2 possesses both pro-survival and growth suppressive functions. Here, we summarize the genetic lesions of *PARK2* in human cancers and discuss the current knowledge of PARK2 in cancer progression. We further highlight future efforts for the study of PARK2 in cancer.

Keywords PARK2 · Mutation · Deletion · Tumor suppressor · Mitophagy · Metabolism

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Introduction

The *PARK2* (*PARKIN*) gene encodes a RING-between-RING-type E3 ubiquitin ligase which serves as a RING/HECT hybrid [1, 2]. The functions of PARK2 have been implicated in protein turnover, stress response, mitochondria homeostasis, xenophagy [3], metabolism, and many other cellular processes regulating cell growth and survival. Genetically, *PARK2* status is associated with risk of autosomal recessive juvenile Parkinson's disease (ARJPD), leprosy, typhoid, and paratyphoid fever [4–6].

A growing body of evidence also shows the involvement of somatic PARK2 inactivation in human cancers, albeit the association between *PARK2* genotype and cancer susceptibility is still under debate [7]. *Park2*-deficient mice show increased susceptibility to tumorigenesis. PARK2 depletion promotes the proliferation and tumor formation ability of pancreatic cancer cells [8], whereas ectopic PARK2 reduces the in vitro or in vivo growth of cancer cells of various tissue origin [9–14], strongly suggesting a tumor suppressive role of PARK2. Moreover, PARK2 overexpression inhibits the migration and invasion of multiple cancer cells ([9] and our unpublished data). This review aims to summarize recent advances on structure, regulation, and function of PARK2 and its murine models, with the emphasis on cancer-associated lesions and the potential link between PARK2 inactivation and cancer development.

Expression, structure, and regulation of PARK2

PARK2 is ubiquitously expressed [15]. The transcription of PARK2 can be regulated by N-myc, Max, p53, and ATF4 [16–18], and various environmental stimulations, such as nutrients, growth signals, mitochondrial, and ER stresses [18–22]. PARK2 precursor transcripts can be processed by pre-mRNA

splicing factors, TDP-43, and FUS/TLS [23, 24]. Alternative splicing of PARK2 produces multiple tissue-specific variants [15, 25]. Interestingly, an internal in-frame Kozak sequence exists in the full-length PARK2 open reading frame (ORF), which initiates the translation of a special form of PARK2 which lacks the N-terminal ubiquitin-like (UBL) domain.

The PARK2 protein is well conserved from nematodes to humans. Full-length PARK2 consists of four important domains: UBL, RING0 (also known as Unique PARKIN domain), RING1, in-between-RING (IBR) domain, and RING2. Additionally, it contains a class II PDZ domain-binding motif towards the C-terminal end [26], and a newly identified Repressor of PARKIN (REP, also known as tether) fragment between IBR and RING2 [27, 28] (Fig. 1a, b). Structural studies reveal an auto-inhibited conformation of PARK2 through complex intra-molecular interactions [27–30]. Briefly, the UBL domain binds to the linker region between IBR and RING2 to stabilize the quaternary structure of PARK2. REP associates with RING1 at the E2 binding site to block E2 recruitment. RING0 intervenes between RING1 and RING2 and buries the catalytic C431, preventing E2-RING2 ubiquitin transfer and subsequent ubiquitin-ester formation (Fig. 1c). Thus, the activation of PARK2 requires massive conformational changes, and the intrinsic auto-inhibition of PARK2 implicates its strict regulation and important function.

Timely recruitment of substrates and activation are two important aspects to execute the E3 ligase function of PARK2. Phosphorylation (S65), oligomerization, and ligand and/or E2 binding contribute to PARK2 activation [27, 30, 31], whereas the phosphorylations catalyzed by c-Abl (Y143) and Cdk5 (S131) attenuate its activity [32–34] (Fig. 2a). Additionally, phosphorylation of PARK2 may modulate its folding, solubility, and ligand or substrate binding affinity [35–37]. To date, posttranslational modifications and interaction partners of PARK2 have been extensively studied [38]. However, the mechanism of PARK2 activation, how PARK2 transits between active and inactive modes, and what determines the specificity of PARK2 remain largely unclear.

Inactivation of PARK2 in cancer

Mutation

Mutations of *PARK2* occur in both ARJPD and solid tumors. Based on the analysis of recent next generation sequencing data via cBio [39, 40], the frequency of *PARK2* mutations is relatively high in cervical cancer (5.6 %), lung squamous cell cancer (5.6 %), colorectal cancer (2.4~5.6 %), gastric cancer (4.6 %), skin cutaneous melanoma (3.5 %), lung adenocarcinoma (2.7~3.1 %), and endometrioid cancer (2.1 %). In addition, several cancer cell lines harboring *PARK2* mutations have been identified (Supplementary Table 1). Most cancer-derived *PARK2* mutations are located at conserved regions (Fig. 2b), and more than 10 % of mutations lead to frame shifts or truncations, suggesting that those mutations may disrupt or abolish the function of PARK2. Notably, several sites mapping to various domains are recurrently mutated, such like A46, T173, T240, P294, P343, Q347, A371, and E395 (Fig. 2b, c). The biological consequences of those mutations need further clarification.

Copy number alterations

Loss of heterozygosity and copy number loss of *PARK2* are found in breast cancer [15], clear cell renal cell carcinoma (ccRCC) [41], esophageal adenocarcinoma [42], glioma [12, 43], non-small cell lung cancer [14], lung adenocarcinoma [44], ovarian cancer [15], and pancreatic adenocarcinoma [8] (Table 1). Further analysis based on recent cancer genomic studies reveals that *PARK2* deletion is also prevalent in adenoid cystic carcinoma (10 %), skin cutaneous melanoma (3.5 %), ovarian cancer (3.2 %) [39, 40], gastric cancer [45], and triple-negative breast cancer (6 %) [46], suggesting that copy number loss is another leading genomic defect of *PARK2*.

Promoter hypermethylation

Promoter hypermethylation is a common epigenetic mechanism to alter the gene expression. *PARK2* promoter hypermethylation has been found in acute lymphoblastic leukemia (ALL, 26 %), chronic myeloid leukemia (CML, 3 %) [47], and colorectal cancer (4.7 %) [10]. 5-Aza treatment could restore the expression of PARK2 in ALL cell lines with *PARK2* promoter aberrant methylation. Interestingly, among 10 samples of CML with lymphoid blast crisis, two showed *PARK2* promoter hypermethylation. To date, the function of PARK2 in the pathogenesis of leukemia remains unexplored. Although the frequency of *PARK2* promoter hypermethylation is low when compared with mutation or deletion, it may serve as an alternative way to inactivate PARK2.

mRNA/protein aberrant expression

As a result of genomic and epigenetic inactivation, the mRNA expression level of PARK2 is downregulated in a wide spectrum of human malignancies (Table 1). In addition, our unpublished analysis of TCGA dataset supports that the mRNA of PARK2 is significantly lower in ccRCC, bladder urothelial cancer, head and neck squamous cell carcinoma, lung adenocarcinoma, breast cancer, thyroid cancer, and endometrioid cancer compared with corresponding normal tissues [39, 40]. Notably, low transcription of PARK2 correlates with increased lymph node metastasis, higher tumor grade, and worse overall survival in ccRCC [48].

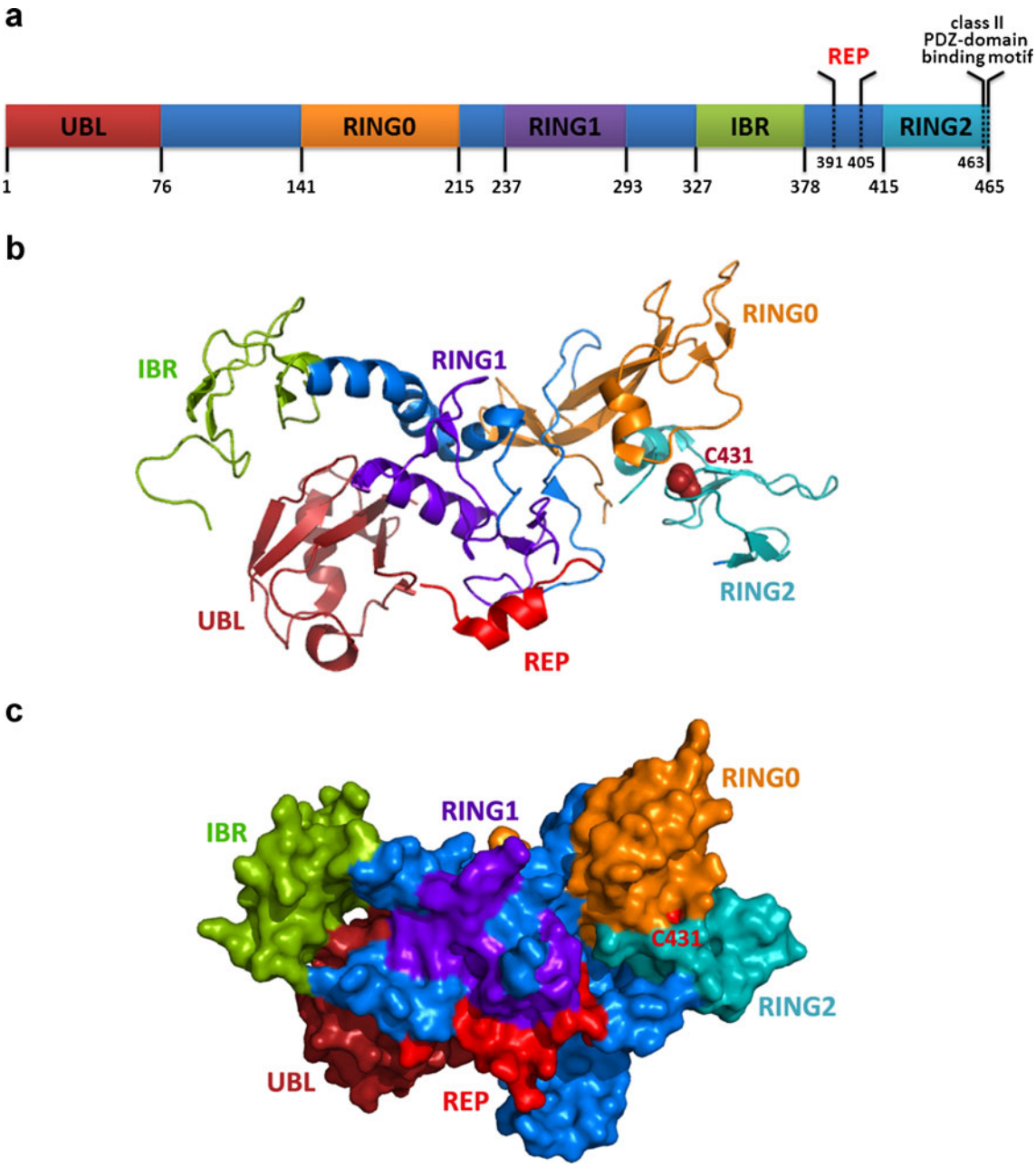

Fig. 1 Schematic and spatial illustrations of PARK2 structure. **a** Functional domains of PARK2 protein. **b** Structure of full-length PARK2 (PDB 4K95). **c** Surface representation of full-length PARK2 (remodeling of PDB 4K95) indicating complex intra-molecular interactions and buried catalytic C431

In parallel to mRNA underexpression, PARK2 protein has been shown to be downregulated in a large panel of cancer cell lines [9–13, 15, 49] and primary tumors (Table 1) [8, 13, 48, 50]. In pancreatic cancer, PARK2 expression is negatively correlated with grade and lymph node metastasis [8]. In breast cancer, PARK2 levels can predict the outcome of paclitaxel treatment [51]. Interestingly, stromal PARK2 abundance is remarkably reduced in malignant breast tissues [9], suggesting a potential role of PARK2 in tumor microenvironment.

Aberrant or alternative splicing may also lead to PARK2 abnormal expression. Aberrant transcripts have been identified in ovarian cancer (15 %) [15], colorectal cancer (42 %) [22], and several CML or cancer-derived cell lines [47, 49, 52], which may result in the disruption of PARK2 ORF and protein function.

Together, genetic and epigenetic disruptions of PARK2 are prevalent across human malignancies, suggesting that PARK2 inactivation may be a driving event during neoplastic transformation and progression.

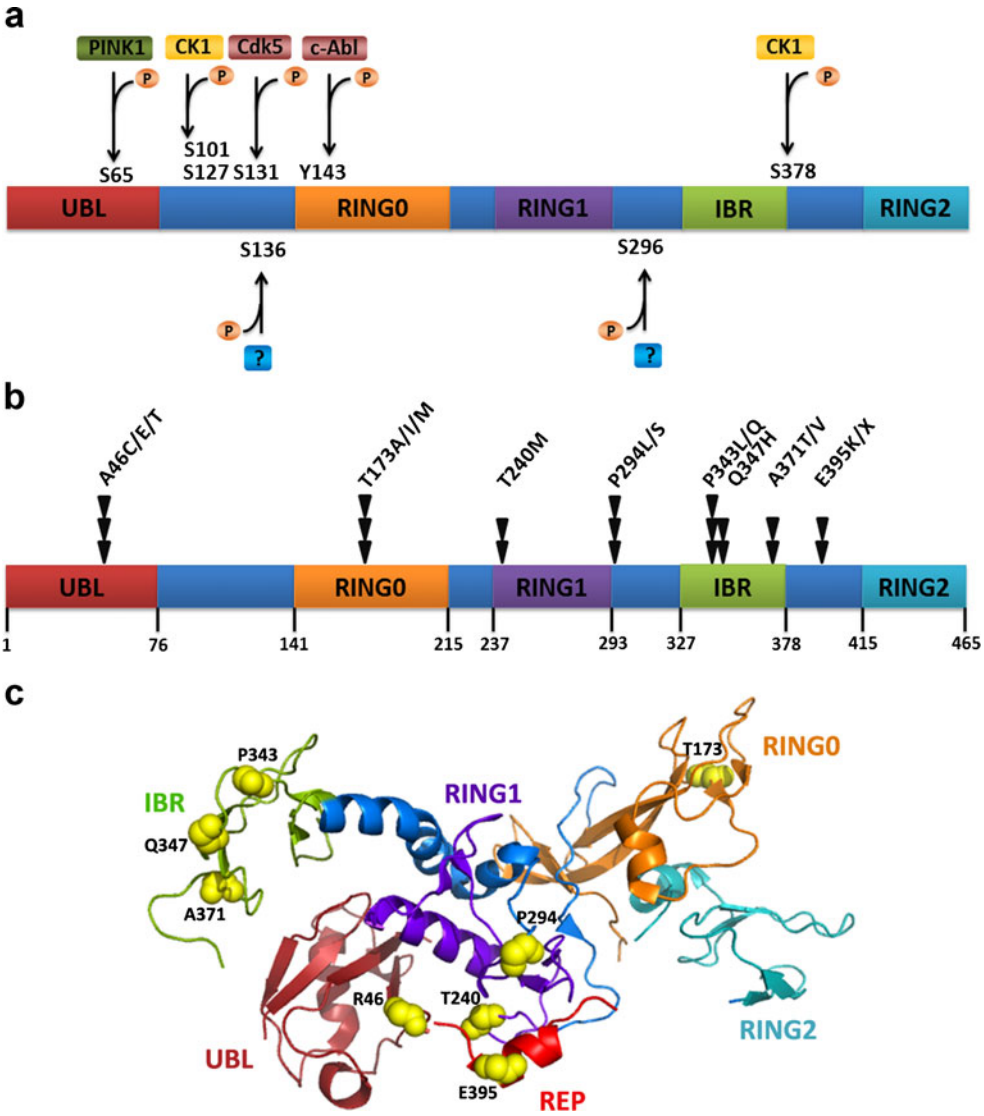

Fig. 2 Phosphorylation and cancer-derived recurrent mutations of PARK2. **a** Sites of PARK2 phosphorylated by various kinases including PINK1, c-Abl, Cdk5, and CK1. **b** Schematic representation of recurrent mutations of PARK2 in cancer. **c** Mapping of cancer-derived recurrent mutations onto the PARK2 structure

PARK2 and tumorigenesis in animal models

Animal models have helped to investigate the role of PARK2 in tumorigenesis. To date, seven lines of *Park2* knockout mice have been generated in an attempt to reproduce Parkinson's disease [53–59]. Generally, *Park2*$^{-/-}$ mice develop normally and do not show a severe neurodegeneration phenotype or obvious clinical defects [60].

However, *Park2*$^{-/-}$ mice are more susceptible to γ-irradiation-induced tumorigenesis [17]. After irradiation, *Park2* is specifically elevated in mouse spleen and thymus in a p53-dependent manner. *Park2*$^{-/-}$ mice show significantly shorter γ-irradiation-induced tumor latency compared with wild-type littermates, even though the tumor spectrum is similar (with the predominant type being lymphoma).

Adult *Park2* null mice show reduced body weight but enlarged livers compared to wild-type mice [61]. Notably, *Park2*$^{-/-}$ mice develop spontaneous hepatocellular carcinoma (HCC) at advanced age [61]. Those tumors histologically recapitulate human HCC with prominent expression of α-fetoprotein and β-catenin. In mouse liver, *Park2* is a lipid-responsive gene whose expression facilitates the lipid uptake of hepatocytes and maintains the systematic lipid metabolism [21]. Whether the dysfunction of liver metabolism contributes to the subsequent hepatocellular carcinogenesis in *Park2*$^{-/-}$ mice is unclear.

Park2 deficiency also promotes colorectal adenoma development [10]. *Park2*$^{+/-}$; *Apc*$^{+/min}$ mice show higher incidence (fourfold increase) of adenomas, and earlier onset of intestinal neoplasia compared with *Park2*$^{+/+}$; *Apc*$^{+/min}$ littermates. The wild-type allele of *Park2* is retained in most adenomas derived from *Park2*$^{+/-}$; *Apc*$^{+/min}$ mice, suggesting that *Park2* may be a haploinsufficient tumor suppressor.

Notably, *Park2*$^{-/-}$ mice develop liver cancer only at advanced age (72 weeks or older) [61], and *Park2*$^{+/-}$; *Apc*$^{+/+}$ mice do not develop intestinal adenoma [10], suggesting that *Park2* deficiency alone may not be sufficient to drive rapid

Table 1 Summary of PARK2 lesions in human malignancies

Type of lesions	Type of malignancies (percentage)	Methods	Refs/database
Mutation	CRC (1.2~2.3 %); GBM (9.3 %); lung cancer[a] (6.5 %)	Sanger sequencing/NGS	[10, 12]
	Cervical cancer (5.6 %); endometrioid cancer (2.1 %); lung squamous cell cancer (5.6 %); CRC (2.4~5.6 %); gastric cancer (4.6 %); skin cutaneous melanoma (3.5 %); lung adenocarcinoma (2.7~3.1 %)	NGS	cBio [39, 40]
mRNA downregulation	Breast cancer[b]; ccRCC (52.1~57 %); GBM (61 %); pancreatic adenocarcinoma (100 %)	qRT-PCR	[8, 9, 41, 43, 48]
	ALL[b]; breast cancer (94.4 %); CML[b]; NSCLC (55 %); ovarian cancer (46.7~50 %)	Semi-qRT-PCR	[14, 15, 47, 52]
	Bladder urothelial cancer[b]; breast cancer[b], ccRCC[b]; endometrioid cancer[b]; HNSCC[b]; lung adenocarcinoma[b], thyroid cancer[b]	cDNA microarray	cBio [39, 40]
	Breast cancer[b]; CRC[b]	RNA-sequencing	cBio [39, 40]
mRNA upregulation	ccRCC (10.6 %); NSCLC (11 %); ovarian cancer (10 %)	Semi-qRT-PCR	[14, 15, 48]
Protein downregulation	HCC (83.3 %); ovarian cancer (71.4 %)	WB	[13, 49]
	Breast cancer (stromal tissue) (100 %); breast cancer (13 %); ccRCC (82.8 %); pancreatic adenocarcinoma (76 %)	IHC	[8, 9, 48, 50]
Promoter hypermethylation	ALL (26 %); CML (3 %); CRC (4.7 %)	MSP	[10, 47]
Gene breakage	Breast cancer (6 %)	FISH	[50]
LOH	Breast cancer[b]; NSCLC[b]; ovarian cancer[b]	MSM	[14, 15, 52]
Copy number loss	Pancreatic adenocarcinoma (100 %)	qPCR	[8]
	CRC (33 %)	aCGH	[10]
	ccRCC (27 %); CRC (24.4 %); esophageal adenocarcinoma[b]; GBM (24.5~29.1 %); gastric cancer[b]; lung adenocarcinoma (11.6 %); triple-negative breast cancer (6 %)	SNP chip	[12, 41–46]
	Adenoid cystic carcinoma[c] (10 %); skin cutaneous melanoma (3.5 %); ovarian cancer (3.2 %)	SNP chip/NGS	cBio [39, 40]
Abnormal splicing	CRC (42 %); ovarian cancer (15 %)	RT-PCR	[15, 22]

ALL acute lymphoblastic leukemia, *CML* chronic myeloid leukemia, *ccRCC* clear cell renal cell carcinoma, *CRC* colorectal cancer, *FISH* fluorescence in situ hybridization, *GBM* glioblastoma multiforme, *HCC* hepatocellular carcinoma, *HNSCC* head and neck squamous cell carcinoma, *IHC* immunohistochemistry, *LOH* loss of heterozygosity, *MSM* microsatellite marker analysis, *MSP* methylation-specific PCR, *NGS* next-generation sequencing, *NSCLC* non-small cell lung cancer, *SNP* single nucleotide polymorphism, *WB* western blot

[a] The detailed subtype was not clear

[b] The exact percentage was not revealed or could not be calculated

[c] The percentage was estimated on the basis of NGS data

neoplastic transformation. Since PARK2 is critical for mitophagy (selective autophagy to degrade damaged mitochondria [62–64]), liver-specific spontaneous tumor formation in *Park2* null mice may result from the long-term toxic effect of mitophagy and/or autophagy defects. A similar phenotype is observed in both *Becn1*$^{+/-}$ and *Atg5*$^{f/f}$; CAG-Cre mice with their advancing age [65–67].

Involvement of PARK2 in cancer associated signaling pathways

Microtubule organization

Microtubules are critical for diverse cellular processes and have been targeted for cancer therapy for decades. The microtubule filaments are composed of α- and β-tubulin heterodimers. PARK2 co-localizes with microtubules and possesses three independent microtubule/tubulin binding domains, including RING0 (together with linker region between UBL), RING1, and RING2 [68]. PARK2 promotes the polymerization of microtubules, thereby increasing their stabilization in cooperation with paclitaxel treatment, and antagonizing the effect of depolymerizing drugs. In response to microtubule-depolymerizing drugs, PARK2 also suppresses the subsequent activation of microtubule-associated protein kinases (MAPKs) including JNK, ERK, and p38 [69]. Ectopic expression of PARK2 sensitizes breast cancer cell lines to paclitaxel, docetaxel, and epothilone B. Moreover, the PARK2 level correlates with the paclitaxel sensitivity in primary breast cancer cells and predicts the response of paclitaxel treatment in breast cancer [51].

On the other hand, PARK2 also acts as an E3 ligase of α/β-tubulins [70]. Interestingly, all of three microtubule/tubulin binding domains and several E3 ligase-deficient PARK2 mutants are able to rescue the microtubule depolymerizing effect by colchicine [68], suggesting that the microtubule-stabilizing ability of PARK2 is independent of its E3 ligase activity. Further, expression of any one of three domains is sufficient to attenuate the activation of MAPKs upon colchicine and nocodazole treatment [69]. Regarding how PARK2 balances between microtubule stabilization and tubulin degradation, one explanation might be that PARK2 predominantly binds with microtubules and selectively targets misfolded tubulins for proteasomal degradation, similar to the case of DJ-1 [71, 72].

Together, the aforementioned observations suggest that PARK2 is an important regulator of tubulin polymerization and microtubule stability. Of note, ectopically expressed PARK2 suppresses cancer cell migration and invasion in vitro ([9] and our unpublished data). As the dynamics of microtubules have been associated with cell migration [73, 74], PARK2 may negatively regulate cancer cell metastasis through its microtubule-stabilizing activity.

Cell cycle progression

PARK2 appears to play a role in cell cycle progression. A recent study revealed the dynamic subcellular localization of PARK2 during cell cycle progression: in interphase, PARK2 shows perinuclear distribution; in mitotic phase, PARK2 mainly localizes to centrosomes and mitotic spindles; and PARK2 is found at midbody during cytokinesis [8].

Functionally, PARK2 mediates the ubiquitination and degradation of Cyclin E in complex with FBXW7 and Cullin1 [12, 22, 75]. It also downregulates the Cyclin D1 level probably through indirect transcriptional repression ([11] and our unpublished data). Overexpression of PARK2 increases G1-phase arrest and delays mitotic entry [9, 11]. Interestingly, PARK2 upregulates the mRNA level of CDK6 specifically in MCF7 breast cancer cells which leads to the cell cycle arrest and growth suppression [9], suggesting that PARK2 may function in a cell type-specific- or context-dependent manner.

PARK2 depletion increases the cell fraction in S- and G2-M phase [12]. Multiple lines of evidence indicate that PARK2 also regulates centrosome and mitotic spindle partially through interaction with γ-tubulin, a protein with well-established function in nucleation and orientation of microtubules [76–78]. The PARK2/γ-tubulin complexes are physiologically present in the cytosol, and PARK2 is reversibly recruited to the centrosome through HDAC6 and a microtubule-dependent mechanism after proteasome blockage, suggesting a potential role of PARK2 in centrosome function. As centrosomes contribute to the formation of the mitotic spindle, the inactivation of PARK2 in cancer may promote the dysregulation of cell division. Indeed, knockdown of endogenous PARK2 leads to spindle misorientation [8], and the development of multipolar spindles as well as micronucleus [12]. Similarly, cells with exogenous C-terminal truncation of PARK2 display increased ability to bypass the mitotic arrest induced by nocodazole and show a higher frequency of multinucleation [78], suggesting a defect in spindle assembly checkpoint. In addition, PARK2 may help to maintain the bipolar spindle assembly through transcriptional repression of Eg5 [8, 79], hence facilitates the proper chromosome segregation during cell division. Together, PARK2 safeguards the proper mitosis by ensuring the function and organization of centrosome and spindle, and PARK2 loss may contribute to the development of aneuploidy.

Mitochondria homeostasis

Mitochondria are critical for cell metabolism and cell death whose dysfunction contributes directly to cancer development. Increasing amount of evidence indicates that PARK2 is involved in the turnover and function of mitochondria.

Mitochondrial genome PARK2 binds to mitochondrial DNA (mtDNA), enhances TFAM-mediated mitochondrial transcription, and restores the PGC-1α expression, thereby promoting mitochondria biogenesis [80–82]. Moreover, it protects the mitochondrial genome from reactive oxygen species (ROS)-induced damage and supports mtDNA recovery [81]. Long-term overexpression of PARK2 selectively eliminates mitochondria with deleterious mtDNA mutations, thereby enriching the wild-type mtDNA for normal mitochondrial function [83]. This suggests that PARK2 is important for the maintenance of integrity of the mitochondrial genome, and thus linking PARK2 alterations to tumorigenesis [84–86].

Mitophagy The role of PARK2 in the induction and progression of mitophagy has been extensively studied, leading to some controversy [62–64]. Generally, mitochondrial stress (depolarization) blocks the inner mitochondrial import of PINK1 and triggers its auto-phosphorylation and stabilization [87–89]. The accumulated PINK1 phosphorylates many substrates including PARK2 at S65, thereby stimulating self-association of PARK2 and then recruiting it to depolarized mitochondrial membrane [31, 90, 91]. Upon activation, PARK2 rapidly catalyzes the ubiquitination of a vast array of mitochondrial proteins, such like FIS1, MFN1/2, RHOT1/2, TOMM70A, and many other substrates [63, 92, 93], and separates mitochondria from the microtubule network [94]. The bulky ubiquitination of mitochondrial proteome subsequently recruits adaptor proteins to connect the autophagy machinery and initiates selective autophagy [95–98]. Ultimately, PARK2-dependent mitophagy selectively degrades damaged mitochondria, thereby maintaining a healthy population of mitochondria.

The function of mitochondria is commonly impaired in cancer [99]. Those mitochondria isolated from the brain of *Park2*$^{-/-}$ mice have reduced respiratory capacity [100], suggesting that PARK2 loss undermines the mitochondrial energy production. However, to what extent PARK2 inactivation contributes to the mitochondria impairment in cancer remains uncertain.

Apoptosis pathway

PARK2 alters the intrinsic mitochondrial threshold for cytochrome c release, thereby protecting cells from apoptotic stress [101, 102]. However, the presence of PARK2 in the mitochondria is not sufficient to prevent cytochrome c release, suggesting that the anti-apoptotic function of PARK2 may be indirect, probably mediated through cytosolic factors. Indeed, PARK2 is capable to regulate the activity of several proteins belonging to the pro- and anti-apoptotic BCL-2 family, including BAX, MCL1, and BCL-2 [92, 103–105]. Of note, after apoptosis onset, PARK2 is cleaved by caspase 1 and caspase 8 [106, 107]. However, compared to the well-established protective function in neurons, the role of PARK2 in regulation of cancer cell apoptosis remains elusive. In cancer cells derived from the liver or breast, PARK2 expression augments the apoptotic cell death induced by HDAC inhibitors and microtubule-stabilizing drugs [13, 51]. *Park2*$^{-/-}$ hepatocytes are more resistant to anticancer drugs than the wild-type counterpart [61]. Additionally, PARK2 sensitizes Hela cells to TNF-α-induced apoptosis [108]. Together, these observations suggest that PARK2 generally exerts an anti-apoptosis function but it also sensitizes cancer cells to certain stimuli.

Cancer cell metabolism

Warburg effect Reprogramming energy metabolism is one of the hallmarks of cancer [109]. During malignant transformation, cancer cells switch from mitochondrial respiration to aerobic glycolysis to sustain the bioenergetics and biosynthetic requirement (known as Warburg effect). PARK2 is a p53 target gene and negatively regulates glucose uptake, oxygen consumption, glycolysis, and lactate production, mitigating the Warburg effect [17]. The mechanism underlying the inhibitory activity of PARK2 may be mediated by regulating the mitochondrial function as well as the expression/activity of metabolic enzymes. Proteomic studies have identified many metabolic enzymes which might be regulated by PARK2 [92, 100, 110–112], albeit the functional consequences of most alterations need to be further clarified. As an example, PARK2 positively regulates the expression of PDHA1, which reduces mitochondrial oxidative phosphorylation and promotes glycolysis [17, 100].

Antioxidant defense *Park2* mutant flies or mice show defects in antioxidant defense [100, 113–115]. Consistently, ectopic PARK2 expression reduces the ROS level and increases the glutathione (GSH) level in cells [17, 116], while PARK2 mutants decrease the GSH and elevate the intracellular oxidative damage [117]. Thus, loss of PARK2 may contribute to ROS production during oncogenic transformation, similar to the effect of p53 inactivation. Paradoxically, PARK2 activity may be required for KRAS-driven tumors to maintain mitochondrial quality control and buffer the oxidative stress, since functional mitochondria and mitochondrial ROS generation

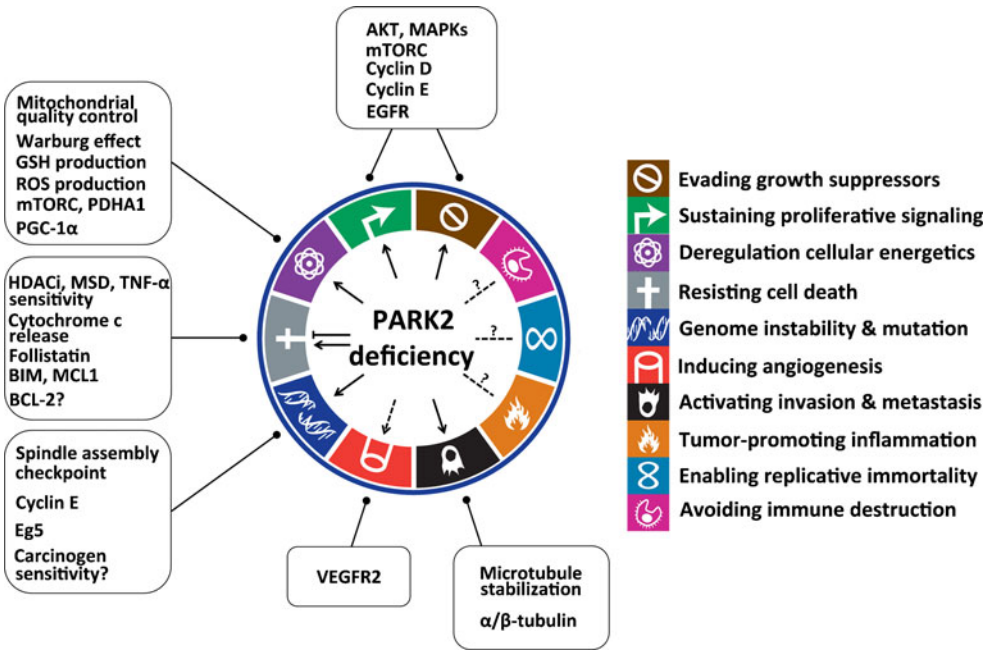

Fig. 3 Mapping targets and/or pathways associated with PARK2 deficiency to cancer hallmarks defined by Hanahan and Weinberg [109]. *MSD*, microtubule-stabilizing drug

are essential for the growth of those tumors [118, 119]. In such a context, PARK2 becomes a pro-survival protein in KRAS-transformed cancer cells. On the other hand, excessive ROS modulates the sulfonation, protein folding, and solubility of PARK2, and thus represses its activity [120–123].

PARK2 in the receptor tyrosine kinase pathway

PARK2 interacts with Eps15 and EGFR upon EGF treatment [124]. Thus, loss of PARK2 might accelerate EGFR endocytosis and degradation, and decrease the EGFR-AKT signaling. However, overexpression of PARK2 in glioma cells paradoxically inhibits signaling through AKT/mTOR [11]. Our unpublished data also support the role of PARK2 as a negative regulator of the EGFR-AKT pathway in gliomas, suggesting a differential behavior of PARK2 in cancer cells. Moreover, PARK2 is able to downregulate VEGFR2 in gliomas [11]; thus, it may have a role in suppression of cancer angiogenesis.

Conclusions and future perspectives

As discussed above, although many aspects remain unexplored, recent data highlight the auto-inhibited structure of PARK2 and uncover its important roles in multiple cellular processes relevant to neoplastic transformation and malignant progression, such like cell cycle control, mitochondria homeostasis, and metabolism (Fig. 3). Importantly, advances in cancer genetics reveal frequent inactivation of PARK2 in a broad panel of human cancers. Murine studies further support the tumor suppressive role of PARK2 [10, 17, 61]. However, characterization of the putative roles of PARK2 in cancer still awaits further efforts as outlined below.

As an E3 ligase, the substrates of PARK2 involved in tumorigenesis remain largely unknown. Apparently, many lessons can be learned from its role in neuron, including its involvement in key signaling pathways implicated in both neurodegeneration and tumorigenesis, such as NF-κB, Wnt, JNK, and estrogen-related receptor pathways [125–129]. Importantly, transcriptomic and proteomic approaches are required to profile systematically the targets of PARK2 in cancer. In addition, deciphering the functional importance of cancer-associated PARK2 mutations is fertile ground of study.

Moreover, knowledge concerning the regulation of PARK2 needs to be expanded. The transcriptional and posttranslational regulation of PARK2 in cancer is unclear, though both are very likely to be impaired. For example, the association between expression and/or activity of PARK2 and the cellular status of p53, N-myc, and c-Abl in human malignancies has not been determined. How does PARK2 shuttle among different cellular compartments? What coordinates the mitochondrial dependent- and independent-function of PARK2? And to what extent do these dysregulations contribute to cancer?

Additional genetic and in vivo studies, including animal models, are essential to dissect further the function of PARK2 during tumorigenesis. Notably, *Park2* deficiency is likely to increase the risk of cancer during exposure to carcinogens or tumor suppressor inactivation [10, 17], suggesting that murine models of *Park2* knockout and other oncogenic background may help to clarify its involvement in tumorigenesis. Meanwhile, the role of PARK2 in "mitochondria-addicted" tumors, especially in RAS/RAF-driven tumors needs further study, perhaps by crossing *Park2* null mice with *Ras*/*Raf* transgenic or knockin mice. Also, generation of *Park2*-associated tumor models will be a powerful tool to test the in vivo efficacy of small molecules modulating the PARK2 pathway, such as vitamin K_2 [130]. Understanding the mechanism of PARK2 activation and function will therefore provide more insights into the development of cancer therapy by targeting the PARK2 pathway.

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Conflict of interest The authors declare no conflict of interest related to this study.

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