Biochimica et Biophysica Acta 1846 (2014) 590–598

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

PINK1 signalling in cancer biology

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ARTICLE INFO

Article history:
Received 20 June 2014
Received in revised form 29 September 2014
Accepted 20 October 2014
Available online 23 October 2014

Keywords:
PINK1
Cancer
Mitochondrial homeostasis
PI3-kinase/Akt
Chemoresistance
Cell cycle

ABSTRACT

PTEN-induced kinase 1 (*PINK1*) was identified initially in cancer cells as a gene up-regulated by overexpression of the major tumor suppressor, PTEN. Loss-of-function mutations in *PINK1* were discovered subsequently to cause autosomal recessive Parkinson's disease. Substantial work during the past decade has revealed that PINK1 regulates several primary cellular processes of significance in cancer cell biology, including cell survival, stress resistance, mitochondrial homeostasis and the cell cycle. Mechanistically, PINK1 has been shown to interact on a number of levels with the pivotal oncogenic PI3-kinase/Akt/mTOR signalling axis and to control critical mitochondrial and metabolic functions that regulate cancer survival, growth, stress resistance and the cell cycle. A cytoprotective and chemoresistant function for PINK1 has been highlighted by some studies, supporting PINK1 as a target in cancer therapeutics. This article reviews the function of PINK1 in cancer cell biology, with an emphasis on the mechanisms by which PINK1 interacts with PI3-kinase/Akt signalling, mitochondrial homeostasis, and the potential context-dependent pro- and anti-tumorigenic functions of PINK1.

Contents

1. PINK1 and cancer overview

PTEN-induced kinase-1 (*PINK1*), a serine/threonine kinase, was identified in 2001, named because it was up-regulated by exogenous expression of the major tumor suppressor, PTEN [1]. Shortly thereafter PINK1 expression was described to be higher in mouse cancer cell lines with higher metastatic potential [2] and a decade ago Valente et al. discovered that loss-of-function mutations in *PINK1* cause autosomal recessive forms of Parkinson's disease (ARPD) [3]. A wealth of research on PINK1 function in neuronal and other cell systems has since emerged accentuating the role of PINK1 in cell survival, stress resistance, mitochondrial function and bioenergetics [4–10].

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http://dx.doi.org/10.1016/j.bbcan.2014.10.006
0304-419X/

The focus of PINK1 research has been centred primarily on understanding Parkinson's disease (PD). However, through this research the PINK1 signalling system has been shown to control several processes key to cancer cell biology. This review discusses the research evidence supporting the association of PINK1 with cancer, focusing on the relationship between PINK1 and the PI3-kinase/Akt pathway, its involvement in stress- and chemo-resistance and the function of PINK1 in key mitochondrial processes which regulate survival/death decisions in cancer cells.

2. PD, neurodegeneration and cancer: common mechanisms balance death and survival

Cancer and neurodegeneration are two pathologic diseases commonly associated with ageing resulting from excessive signalling by opposing forces: those promoting cell survival and cell death, respectively. This commonality of signalling systems that balance cell death or survival choices has been highlighted with respect to PD and cancer [11–17]. Thus, many molecular processes and signalling systems are common to both diseases, including: cell cycle control, DNA repair, mitochondrial dynamics/metabolic control, proteostasis, and a number of master signalling pathways, in particular the PI3-kinase/Akt system [12,15–18].

The cross-talk between cancer and neurodegeneration is supported by epidemiological studies which indicate reduced risk of certain cancers in patients diagnosed with neurodegenerative diseases [18,19]. This inverse correlation between neurodegeneration and cancer risk is especially notable for PD [16], where reduced risk of most cancers is reported [20], with the exception of malignant melanoma [21–23]. Importantly also, several of the genes discovered to cause inherited autosomal dominant or recessive PD, including PINK1, have been described to have both oncogenic and tumor suppressor properties [11,15,17,20,24–26].

3. PINK1 function overview

The *PINK1* gene contains 8 exons and encodes a 581 amino acid protein consisting of an N-terminal, non-canonical mitochondrial targeting sequence (MTS), a transmembrane domain, a highly conserved serine/threonine kinase domain and a C-terminal autoregulatory sequence [27,28]. PINK1 displays homology with the Ca^{2+}/calmodulin family of protein kinases, most closely related with CaMKI, CaMKII and dystrophia myotonica protein kinase (DMPK) [28]. PINK1 is expressed ubiquitously, and localises to mitochondria and cytosol [29] with highest levels reported in the central nervous system (CNS), heart, testis, liver and skeletal muscle [1,30–34].

Research during the past decade demonstrates that PINK1 has major pro-survival, anti-apoptotic and cytoprotective functions [35–44]. These properties of PINK1 have been shown to be implemented by both mitochondrial and cytosolic functions of PINK1, and mechanistically through proteasomal [45–47] and autophagic [48,49] pathways, and via PI3-kinase/Akt/mTOR [37,41,50,51], NFκB [52,53] and calcium dependent signalling [54–56]. Moreover, PINK1 has a primary function in mitochondrial homeostasis and dynamics, including mitophagy, bioenergetics, fission and fusion [49,54,57–70].

Many of the systems PINK1 regulates converge on stress resistance and cell survival, and several studies now support a role for PINK1 in cancer cell biology [1,24,37,39,71–73]. PINK1 protein expression in cancer tissues ranges from high in breast, colorectal and endometrial to low in sarcomas, neuroblastomas and leukemias, and within this setting, PINK1 has been purported to have a dual role in cancer biology, with context dependent pro- and anti-tumorigenic properties [24]. This is supported by meta-analysis of PINK1 mRNA expression in cancer datasets (Oncomine, COSMIC databases), where PINK1 expression is significantly decreased in several different malignancies including ovarian, liver and renal carcinomas, while being significantly overexpressed in a subset of renal, endometrial, haematopoetic and parathyroid cancers. In addition, a small number of heterozygous mutations in PINK1 have been identified in some cancers including endometrial, oesophageal and ovarian (COSMIC database), all of which are different to the known ARPD-causing mutations, though their functions remain to be explored. PINK1 mutations (Leu437Pro; Arg279His), were also identified as rare germline variants predisposing to neuroblastoma, [74]. These mutations have been identified as heterozygous rare variants that occur in idiopathic PD, whose significance is uncertain [75–77]. The *PINK1* gene itself is located on chromosome 1p36 [1,78], a site which is frequently deleted in a broad range of cancers and has been postulated to harbour one or multiple tumor suppressors [79].

4. PINK1 and the PI3-kinase/Akt signalling axis in cancer

4.1. Synopsis of PTEN and the PI3-kinase/Akt system in cancer

The discovery and naming of *PINK1* as a gene induced by overexpression of *PTEN* [1] linked PINK1 with tumor suppression and regulation of the PI3-kinase/Akt signalling from the first instance. The lipid and protein phosphatase *PTEN* is one of the most frequently mutated genes in human cancers [80], including glioblastoma, endometrial, breast and prostate cancers, earning it the alias mutated in multiple advanced cancers (MMAC1) [81]. Germline *PTEN* mutations are primarily found in Cowden disease, an autosomal dominant multiple hamartoma syndrome [82]. The tumor suppressive functions of PTEN are mediated in a number of ways but primarily by inhibition of PI3-kinase/Akt signalling, a major oncogenic pathway. Akt, a serine/threonine kinase (also known as Protein kinase B (PKB)) is activated by growth factors, insulin, cytokines and cellular stressors including reactive oxygen species (ROS).

Akt is a major driver of tumorigenesis, enhancing cellular growth, proliferation, motility and protection from apoptosis [83,84]. In addition, Akt regulates cellular metabolism [85], critical for cancer cell survival and anaerobic glycolysis allowing metabolic rewiring of glycolysis and mitochondrial function [86–89]. Akt phosphorylates a myriad of downstream substrates, including glycogen synthase kinase β (GSK3β), forkhead box (FOXO) family of transcription factors and mammalian target of rapamycin (mTOR) complexes (mTORC1 and mTORC2). The variety of Akt substrates, some of which are activated, some of which are inactivated by phosphorylation by Akt, make it a signalling node on which many cellular functions hinge [90].

PI3-kinase/Akt signalling is intimately linked with mitochondrial respiration, glucose metabolism, prevention of mitochondrial apoptosis, and enhanced glycolysis in cancer cells. Akt phosphorylates hexokinase II [91], promoting its association with the voltage dependent anion channel (VDAC) and subsequent channelling of mitochondrially-produced ATP for glucose metabolism, proposed to underlie the Warburg effect [85,89]. Furthermore, Akt directly phosphorylates both pro- and anti-apoptotic mitochondrial proteins such as Bcl-2-associated death protein (Bad) and the inhibitor of apoptosis proteins (XIAPs) to inhibit mitochondrial apoptosis [89]. Akt has also been shown to drive mitochondrial respiration through mTORC1-induced protein translation of respiratory complexes [92] and via mTORC2/Akt signalling in mitochondrially-associated endoplamic reticulum membranes (MAMs) regulating growth, mitochondrial function and metabolism [93].

Indeed, due to its multitudinous function in cancer, PI3-kinase/Akt signalling is a major target of a plethora of anti-cancer drugs, such as BKM120 which inhibits PI3-kinase, sirolimus (rapamycin), which targets mTOR and the dual PI3-kinase/mTOR-targeting BEZ235 [94,95].

4.2. PINK1 and the PI3-kinase/Akt signalling in cancer

4.2.1. Overview

Since the initial study naming PINK1 due to its induction by PTEN in cancer cells, significant attention has been drawn to the interaction between PINK1 and the PI3-kinase/Akt signalling system [35,37,41,96,97]

at multiple interconnected levels that impact cancer biology (Fig. 1). In sum, PINK1 can directly activate Akt via activation of mTORC2 to enhance cancer cell invasiveness [37] and promote cancer stem cell renewal via Notch signalling [50,98]. In HeLa cells, PINK1 induces Akt phosphorylation of hexokinase-II at the mitochondria, resulting in increased anaerobic glycolysis [99]. FOXO3a markedly induces human *PINK1* transcription in cancer cells when PI3-kinase/Akt is inhibited and under stress conditions when growth factors and cytokines are withdrawn [35]. In the latter context, PINK1 has been proposed to induce protection from short term stress increasing cell survival, priming cells for Akt activation when the stress is lifted. In the sections below we discuss the interactions of PINK1 with the PI3-kinase/Akt pathway with direct relevance to cancer in more detail.

4.2.2. PINK1 activation of PI3-kinase/Akt signalling in cancer

PINK1 activates mTORC2, in both cancer cells [37,50] and post-mitotic neurons [51]. This further activates Akt via mTORC2-induced Akt phosphorylation in dividing cells, however Tricornered (Trc)/NDR kinase, rather than Akt activation, has been shown to be the effector-target in post-mitotic neurons in *Drosophila* [51]. The mechanisms of activation of mTORC2 via PINK1 have been shown to differ. Thus, PINK1 activation of mTORC2-Akt can occur in the cytosol via Rictor promoting cellular motility and survival in cancer cells, crucial for protection from various cytotoxic agents [37]. In these studies Rictor, a specific activating component of mTORC2, was phosphorylated by overexpression of PINK1, indicating but not proving, that this may be mechanistically important. In addition, PINK1 activation of mTORC2-Akt via non-canonical Notch signalling was shown to be critical for the preservation of brain tumor forming stem cells, and here mTORC2 activation was shown not to be directly activated by PINK1 via Rictor, but rather to involve PINK1-regulation of mitochondrial respiratory chain complex (RCC) function [50,98].

The relevance of these latter findings to human cancers was shown using patient-derived glioblastoma multiforme (GBM), which exhibited both increased PINK1 and Notch expression, where deletion of PINK1 inhibited proliferation in GBM cancer stem cell cultures. The relevance and context of the differential mechanisms shown to activate mTORC2 downstream of PINK1 need further study to dissect out whether they can occur simultaneously or are mutually exclusive. Importantly, Lee and colleagues point out that the PINK1/mTORC2/Akt effector system linked to RCC regulation may be specific to dividing cells, where their associated work showed a PINK1/mTORC2/Trc effector system maintaining Complex I activity in post-mitotic cells [51]. The, mTORC-2/Akt signalling system regulates mitochondrial physiology and hexokinase-II activation in MAMs [93], controlling growth and energy metabolism in ways that are tumor promoting. In keeping with this, PINK1 activation of Akt leads to its phosphorylation of hexokinase-II, required for PINK1-induced parkin recruitment to mitochondria in cancer cells, as well as increased anaerobic glycolysis, a key feature of tumorigenesis [99].

In addition, PINK1 expression has been shown to be essential for optimal activation of IGF-1R, a major tumor promoter [100] and upstream activator of PI3-kinase/Akt signalling. PINK1 has also been clearly demonstrated to interact and regulate eIF4E-binding protein (4E-BP) [101,102], an essential downstream effector of Akt-mTORC1 which balances 5′cap-dependent protein translation, and cap-independent internal ribosomal entry site (IRE) dependent protein translation, the latter essential for transcription of stress resistant protein module transcription including HIF1α. Although loss of PINK1 prevents the 4E-BP1-dependent switching in protein translation to attenuate HIF1α induction [101] in MEFs, the lack of direct evidence for PINK1 regulation of 4E-BP in cancer cells reduces discussion of this in the context of this review.

Together, the ability of PINK1 to activate Akt, especially via the mTORC2/mitochondrial control axis in cancer cells, suggests that modulating PINK1 may reduce the plasticity of Akt activation responses which are central to the metabolic rewiring that enables cancer cells to thrive both in normal and stress contexts.

4.2.3. PTEN and FOXO induction of PINK1 in cancer cells

Following from its original discovery as a PTEN-induced gene in endometrial cancer cells, recent work has further shown that PINK1 is induced by PTENα, a PTEN isoform translated through alternative initiation [103]. PTENα localised to mitochondria and induced complex IV cytochrome *c* oxidase activity in both the presence and absence of canonical PTEN in both MCF-7 breast and PC3 prostate cancer cells. PTENα was found to interact with PTEN to increase PINK1 expression and promote ATP production. Dissecting the PTEN-induced PINK1 specific

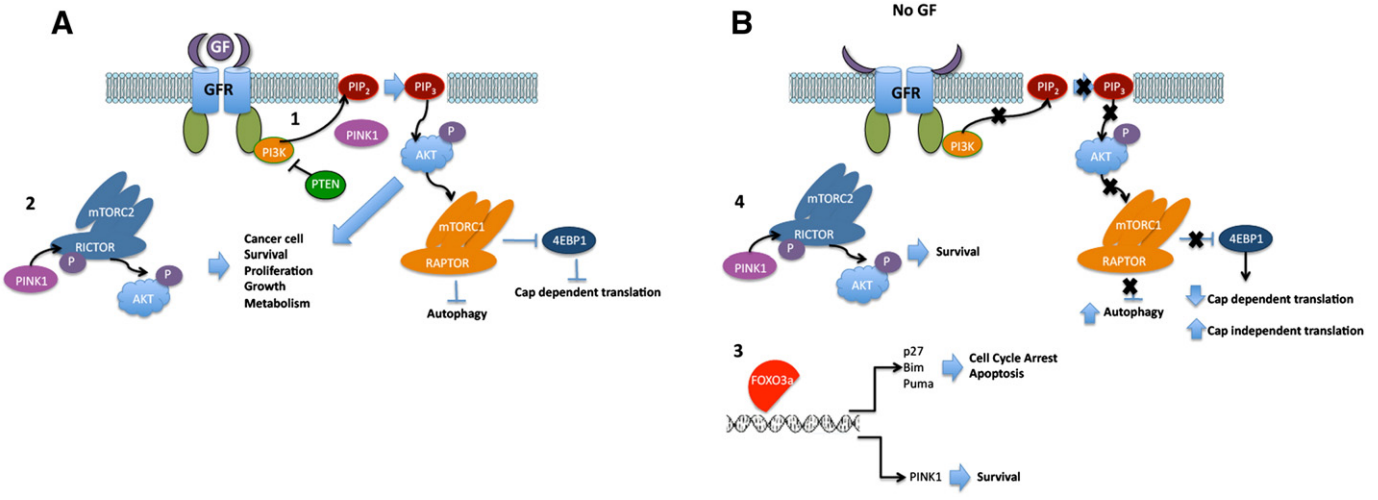

Fig. 1. PINK1 and PTEN/PI3-kinase/Akt signalling implications for growth factor signalling and stress-resistance in cancer cell biology. A. 1. PINK1 expression enhances growth factor (GF), including IGF-1-induced, activation of receptors and downstream targets including the major oncogene Akt. 2 PINK1 also activates Akt independently of growth factor signalling via direct phosphorylation and activation of the mTORC2 subunit Rictor. Both of these effects of PINK1 will increase survival, proliferation and growth of cancer cells. B 3. PINK1 is also induced in stress and growth factor / nutrient deprivation contexts when the PI3-kinase/Akt signal is off, allowing FOXO transcription factors to enter the nucleus and induce stress-response gene networks including PINK1. Specifically, FOXO3a increases the transcription of PINK1. This stress-induced activation of PINK1 enhances cell survival in the presence of stress, including chemotherapeutic stress. This induction may also allow the system to be 'primed' to respond if and when stressors are lifted, most likely through PINK1-induced mTORC2 activation. 4. PINK1 also interacts with mTOR through its regulation of autophagy and protein translation via 4EBP-1 by balancing cap-dependent and independent protein translation. In this way, PINK1 enables the translation of HIF1α and stress resistant networks during hypoxia when 4EBP-1 is inhibited.

functions from the broad tumor suppressor function of PTEN in cancer will be important. In this context, the original studies found that although induced by PTEN, and suggested to be tumor suppressive, overexpression of the PINK1 transcript showed no inhibition of cell growth in a number of cancer cell lines [1]. Indeed, recent work in our lab did find significantly reduced colony growth in MEFs and cancer cells lacking PINK1 [72], indicating a potential role in tumor promotion for PINK1.

In addition to PTEN, PINK1 expression can be induced by FOXO3a, a member of the FOXO family of transcription factors which Akt inhibits. This occurs in cancer cells when PI3-kinase/Akt is inhibited and/or growth factors and nutrients are deprived [35]. The binary switch between Akt and FOXO signals allows the cell to respond rapidly to changing circumstances [84]. The importance of FOXOs in cancer biology has been emphasized [84,104], and murine genetic studies show that broad somatic deletion of all three FOXOs results in a cancer-prone condition dominated by lymphomas and hemangiomas [105]. FOXO3a can act as a bona fide tumor suppressor in renal carcinogenesis, functioning to constrain mTOR signalling [106]. Interestingly, FOXO3a has been shown to promote cancer invasiveness through the upregulation of matrix metallo-proteinases [107].

FOXO induces the transcription of gene networks that allow the PI3-kinase/Akt system to be "primed" if and when the stress is lifted. In this context, it is extremely interesting that FOXO3a induces PINK1 expression during growth factor deprivation [35]. In fact FOXO3a, is the only confirmed transcription factor shown to regulate PINK1 to date, with several FOXO binding elements (FBEs) identified in the PINK1 promoter. As PINK1 is also important for maximal PI3-kinase/Akt signalling [41,96,108], it is thought that PINK1 may be transcribed so that the system is "ready" to be maximally responsive to a returned stimulus, thereby having potential to confer short term protection [35] and stress resistance.

FOXO3a also induces the transcription of several pro-apoptotic proteins, which carry out cell cycle arrest and cell death programmes following a stress event [109]. Though the parallel induction of pro-survival (PINK1) and these pro-apoptotic signals may seem contradictory, it could provide a means for cancer cells to postpone cell death programmes, increasing the threshold for pro-death signals. This could also underlie the chemoresistant function of PINK1. Resistance to chemotherapy is a major challenge in the treatment of cancer, and an RNAi screen of the kinase and phosphatase component of the human genome identified PINK1 as a major pro-survival kinase, loss of which sensitises breast cancer cells to treatment with paclitaxel [39]. Notably FOXO3a expression induces sensitisation to this chemotherapeutic drug [110–112], thus FOXO3a-induced transcription of PINK1 may override this sensitisation and confer chemoresistance. Furthermore, PINK1 deletion increases susceptibility of cancer cells to DNA damage, and is lethal in cancers with DNA mismatch repair (MMR) deficits [113]. This work highlighted PINK1 as a novel therapeutic target in the treatment of DNA MMR-deficient cancers [113]. FOXO transcription factors can prevent DNA damage through induction of expression of DNA repair genes [114], and PINK1 may therefore have a role in this process.

Combined, the findings of the above studies describe major functional links between PINK1 and the PI3-kinase/Akt signalling system, which are of importance for many key areas of cancer cell biology. It would appear that PINK1 can both drive PI3-kinase/Akt/mTOR signalling in cancer cells, conferring cytoprotection and promoting growth, and motility, and also functions as a major stress-resistant gene in cancer when nutrients, growth factors are reduced. In this way, PINK1 functions in a pro-survival role downstream of stress signals, and has been identified as a target for chemoresistant and DNA MMR-deficient cancers.

5. PINK1: mitochondrial homeostasis and cancer

5.1. PINK1 regulation of mitochondrial homeostasis: overview

Extensive research has revealed that PINK1 is a major regulator of mitochondrial homeostasis and mitochondrial bioenergetics. Though much of the research was designed to understand PINK1's regulation of mitochondrial function in Parkinson's disease, many of these studies were in fact carried out in cancer cells such as the cervical adenocarcinoma HeLa [57,115,116] and the neuroblastomas SH-SY5Y [58,65,67,117] and BE(2)-M17 [55]. Overall, PINK1 maintains mitochondrial membrane potential, oxidative phosphorylation [69,118,119], complex I activity [69,117,120], reactive oxygen species (ROS) and Ca^{2+} balance [54], regulates mitochondrial dynamics [58,67,70,121–124], protects from mitochondrial stress [43,58,69,96,125] and is a key regulator of mitophagy [57,60–62,65,115,126–128].

PINK1 function is central to mitophagy and involves the E3 ubiquitin ligase activity of parkin, mutations in which are the most prevalent cause of ARPD (reviewed in [144,148]). A role for PINK1 in mitochondrial dynamics was first highlighted in *Drosophila*, whereby loss of PINK1 causes enlargement and swelling of mitochondria in post-mitotic tissues [68,70,129,130] and overexpression of the mitochondrial fission GTPase dynamin related protein 1 (Drp1) rescues this phenotype [70,129,131], indicating that PINK1 promotes mitochondrial fission or limits mitochondrial fusion in post-mitotic cells. In contrast, deletion of PINK1 in cancer cells, which are actively dividing, causes fission resulting in increased fragmented mitochondria which can be rescued by knockdown of Drp1 [55,58,67,72,132]. These PINK1-regulated mitochondrial quality control mechanisms of fission, fusion and mitophagy are critical regulators of mitochondrial turnover and homeostasis. This is true especially in cancers, where this system shapes cell death and survival decisions for example, mitochondrial fission is a critical step in both apoptosis [133,134] and during mitosis [135–138].

5.2. Mitochondrial homeostasis and cancer

Mounting evidence indicates that mitochondrial defects contribute to the development of malignant cells, including mtDNA mutations, altered metabolic pathways, increased mitochondrial ROS and deregulated mitochondrial dynamics [87,88,139–144]. Altered metabolism is an established hallmark of cancer cells [87,88,141] and recent advances have shown that many other facets of mitochondrial biology, including mitochondrial fission, fusion, and mitophagy contribute to tumorigenesis [145,146]. Mitochondrial DNA (mtDNA) encodes a number of genes, including those responsible for oxidative phosphorylation. mtDNA is more prone to mutations than nuclear DNA, and given the proximity to ROS released due to mitochondrial respiration, is more at risk of contact with DNA damaging species. mtDNA mutations have been found in numerous different cancers [147]. Intracellular ROS, below a certain threshold, can also contribute to survival signalling through activation of a number of signalling pathways including autophagy and PI3-kinase/Akt [141,148].

5.3. PINK1 regulation of mitochondrial fission, fusion and mitophagy: implications for cancer and cell cycle progression

The regulatory function of mitochondrial homeostasis that impacts on cancer cell biology has been shown at multiple levels in cancer cells (Fig. 2). Firstly, as mentioned above, deletion of PINK1 in cancer cells causes fission resulting in increased fragmented mitochondria which can be rescued by knockdown of Drp1 [55,58,67,72,132]. Mitochondrial fission is a critical step in apoptosis in cancer cells, happening early on in the death programme [134,146], and is linked to mitochondrial outer membrane permeabilization (MOMP), regulated by Bcl-2 family proteins, by which cytochrome *c* is released into the cytosol [134]. PINK1 has been shown to prevent this mitochondrial fragmentation, cytochrome *c* release and apoptosis by promoting mitochondrial fusion in cancer cells [67].

At the heart of tumorigenesis and cancer cell proliferation is an active cell cycle, and the triad of mitochondrial fission/fusion and mitophagy and their interrelationship with mitochodrial bioenergetics has been shown to be crucial during cell cycle progression. Specifically,

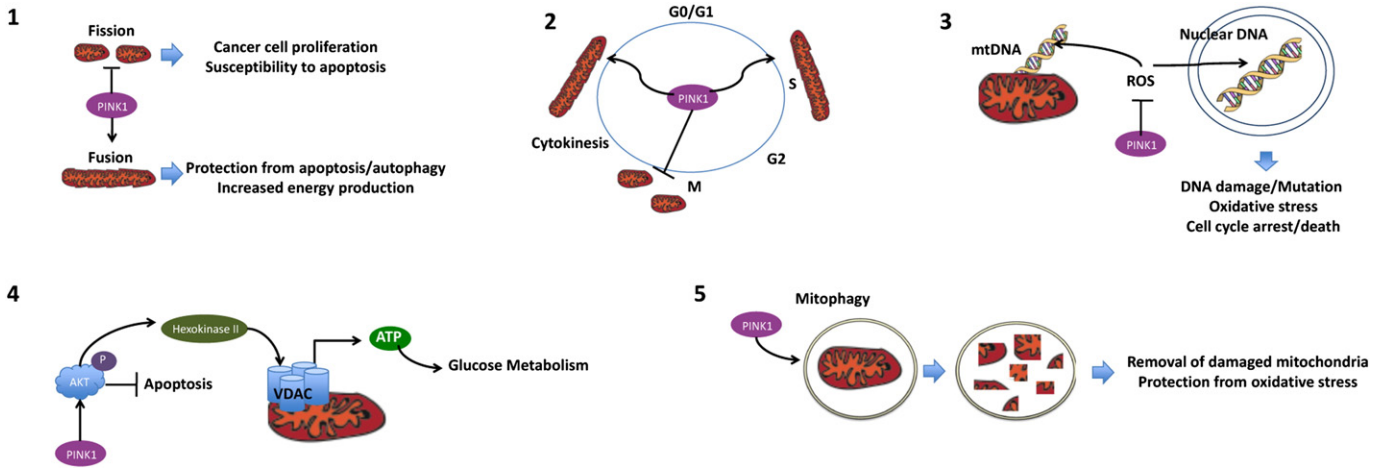

Fig. 2. PINK1, mitochondria and tumorigenesis. 1. PINK1 promotes mitochondrial fusion and prevents mitochondrial fission in dividing mammalian cells, protecting cells from apoptosis, and stress. 2. PINK1-control of the mitochondrial fission/fusion axis promotes effective cell cycle progression at mitosis and during stress and nutrient deprivation, where fused mitochondrial networks alter metabolic bioenergetics and metabolic programmes to enable cell survival. 3. Mitochondrial respiration gives rise to reactive oxygen species (ROS) which can induce oxidative stress, cause damage to both nuclear and mitochondrial DNA and can result in apoptosis. PINK1 expression reduces ROS, prevents DNA damage and protects against apoptosis. 4. Akt directly inhibits pro-apoptotic machinery, and recruits hexokinase II (HKII) to VDAC to induce the shuttling of mitochondrially-produced ATP into the cytosol to participate in glycolysis, thereby aiding in the reprogramming of cellular metabolism known as the Warburg effect. PINK1 enhances Akt activation, and may therefore contribute to this metabolic switch. 5. Damaged mitochondria are removed from the cell via mitophagy, preventing the build-up of ROS and Ca^{2+} in the cytosol, which can induce cellular damage and apoptosis. PINK1 is the major mediator of mitophagy, clearing damaged mitochondria from the cell to maintain mitochondrial homeostasis. Mitophagy can both promote and prevent tumorigenesis.

mitochondrial fission is critical for cell cycle progression at mitosis [136,137] and during interphase where it regulates Drp1 function [135,149], and contributes to hyperproliferation of vascular smooth muscle cells [150]. Recent work from our lab has revealed for the first time that the regulation of mitochondrial fission by PINK1 is critical for cell cycle progression at key checkpoints (G2/M and G0/G1) necessary for cell division, growth and stress resistance in cancer [72]. These results show that deletion of PINK1, in both MEFs and cancer cells, induces cell cycle arrest during G2/M at cytokinesis blocking nuclear separation and increasing the number of multinucleated cells. Mechanistically, this links to mitochondrial dynamics where absence of PINK1 kinase activity increases mitochondrial fission and Drp1 activation and blocks the mitochondrial fusion necessary to exit mitosis, as well as inducing significant alteration in cell cycle marker profiles. The aberrant increase in mitochondrial fission induced by PINK1 kinase deletion also reduces mitochondrial membrane potential and impaired cell cycle exit at GO/G1 necessary for stress-resistance [72].

Importantly, the above findings directly link the regulation of mitochondrial dynamics by PINK1 with cell cycle progression and cell proliferation in cancer and may conversely underlie the mechanisms through which loss of PINK1 sensitises cells to chemotherapeutic drugs targeting mitotic cells [39]. Targeting PINK1 may thus block the cell cycle and constrain proliferation and stress resistance in certain cancers, albeit that an inability to effectively divide can increase chromosomal aberrations in other cancer types. In line with the former this work found deletion of PINK1 inhibits several cancer causing phenotypes including proliferation, colony formation and migration [72].

PINK1 promotes mitophagy in cancer cells via the ubiquitin ligase parkin [57,60,65,151]. Mechanistically, PINK1 acts as a molecular sensor accumulating on damaged mitochondria with reduced mitochondrial membrane protein [57,60,65,151,152], inducing autophosphorylation of PINK1 [153], selective recruitment of parkin to damaged mitochondria [57,60,65] with PINK1-dependent phosphorylation of parkin [153,154] and ubiquitin [155] initiating parkin's ubiquitin ligase activity to initiate mitophagy.

Mitophagy is a double edged sword in cancer cell biology where the regulation of this process by PINK1 could promote both cell death and survival in cancer. Thus, increased mitophagy clears damaged mitochondria including prior to mitosis, preventing the build-up of ROS and Ca^{2+} inducers of cellular damage and apoptosis in tumor cells thus enhancing survival [156–158]. Conversely, excessive mitophagy can contribute to programmed cell death and be tumor suppressive, where notably parkin, has been shown to be a tumor suppressor [25,26,159]. Likewise, decreased mitophagy causes the accumulation of damaged mitochondria, increased intracellular ROS, can cause DNA and mtDNA mutations [143] and chromosomal aberrations which can both kill cells and can also inappropriately activate survival signals such as the PI3-kinase/Akt pathway [148].

PINK1 recruitment to depolarised mitochondria has also been shown to protect from cell death in cancer cells by phosphorylation of the major pro-survival protein Bcl-xL, preventing Bcl-xL's pro-apoptotic cleavage, and described to be independent of mitophagy [36]. Further, PINK1 deletion reduces Bcl-xL and increases BAX protein expression in bladder cancer cells, linked to their partial sensitisation to cell death [73]. Interestingly, recent studies show that expression of Bcl-xL, as well as other Bcl-2 family members strongly inhibited the elimination of mitochondria via PINK1-parkin induced mitophagy, and could bind to PINK1/parkin complexes inhibiting parkin translocation to mitochondria in cancer cells [160]. Taken together, PINK1's regulation of mitophagy in cancer cells, with interplay with mitochondrial fission/fusion and the Bcl-2 family, places it at centre stage for balancing mitochondrial homeostasis with cell death and survival decisions in cancer cells.

In addition to mitophagy, PINK1 is also associated with the regulation of global cellular autophagy, particularly via association with the autophagic initiator Beclin-1 [48] where it can promote both basal and starvation induced autophagy in cancer cells. As with mitophagy, it is not yet clear as to in which context autophagy helps or prevents tumorigenesis. However, it is abundantly clear that both mechanisms are strongly linked to cancer cell biology [25,87,145,161,162].

In summary, PINK1 influences mitochondrial quality control and bioenergetics in major ways that regulate cancer cell biology, including key points in the cell cycle that are critical for cell division growth and stress resistance. Pro-and anti-tumorigenic PINK1 functions in cancer are most likely caused by the cellular response of PINK1 to outcomes that occur during cell division, DNA repair and stress resistance and how this interplays with regulatory function of PINK1 in mitochondrial quality control and PI3-kinase/Akt signalling.

6. Concluding remarks and future perspectives

PINK1 interacts with a number of signalling networks which are key for cell survival in both cancer and PD, including the interlinked PI3-kinase/Akt/mTOR signalling system, bioenergetic and mitochondrial quality control.

The potentially pro- and anti-tumorigenic properties of PINK1 were highlighted from its first discovery. Thus on the one hand PINK1 was described to be higher in cancers with higher metastatic potential [2] and on the other to be induced by the tumor suppressor PTEN [1]. While much current evidence points to PINK1 as a tumor promoter and mediator of chemoresistance, PINK1 has also been purported to have a dual role in cancer biology, with context dependent pro- and anti-tumourigenic properties [24]. Such pro- and anti-tumorigenic properties are emerging to be common for many proteins, including for example c-Rel [163], CLU [164] and even FOXO3a [107].

PINK1 mutations are found in some but not all cancers while PINK1 expression is increased in some cancer tissues, and decreased in others (24, COSMIC, Oncomine). *PINK1* is located on frequently deleted chromosomal region and is induced by the tumor suppressors PTEN and FOXO3a, though this induction could represent a parallel protective signal in the absence of PI3-kinase/Akt signalling. Furthermore, while deletion of PINK1 inhibits proliferation, colony formation and migration [72] and sensitises cancer cells to a myriad of stressors [37,39,42,113,165,166], in other contexts exogenous overexpression of PINK1 in established cancer cells either has no effect [1] or can inhibit colony formation [24].

From a mechanistic standpoint, the duality of PINK1 function in cancer cell biology may stem from its regulation of mitophagy, which as discussed above may be tumor promoting in some circumstances and tumor suppressive in others, depending on the cellular context. In addition, PINK1's role in cell cycle progression in mitochondrial fission/fusion transitions particularly at mitosis could also be tumor promoting/suppressive depending on the cancer cell and its own adaptations. Thus an inability to progress through cytokinesis as a result of PINK1 deletion will result in cell death [167]. However, failure to properly complete cell division and aneuplody increases the frequency of chromosomal aberrations which can be cancer promoting [168], further highlighting the notion that PINK1 function may have a dual role in cancer.

Intertwined with this is duality of PINK1 regulation of the major oncogenic PI3-kinase/Akt axis. Thus PINK1 can both activate Akt, and regulate its association with mitochodria powering anaerobic glycolysis, and also be induced when the Akt system is turned off via both FOXO and PTEN. The responses to FOXO3a-induction of PINK1 may potentially outwit FOXO to promote stress-induced survival, including chemoresistance in cancer cells or alternatively cause tumor suppression.

In summary, the mechanisms regulated by PINK1 most likely drive stress resistance and cellular health in neurons in PD, but also in cancer cells. While there is evidence for PINK1 as a tumor promoter, the potential duality of PINK1 in cancer biology still needs to be clarified *in vivo*, and under which contexts PINK1 is pro- or anti-tumorigenic. In addition, it will be of interest to determine the significance of PINK1 mutations in human cancers. Hence, PINK1 may either be a promising target for inhibition or a predictive biomarker of response to treatments of cancers, especially those which are resistant to chemotherapy, have DNA damage deficits or are dependent on mitochondrial or autophagic processes for energy. Further attention clearly needs to be given to PINK1 and its role in cancer biology in order to better understand disease mechanisms and to determine in which cancers PINK1 inhibition may be therapeutically beneficial.

Acknowledgements

This work was funded by the Health Research Board of Ireland, PhD Scholars' Programme in Cancer Biology grant number PhD/2007/4. Support from Science Foundation Ireland grant number 07/RFP/BIMF648 (SFI) (RFP) is also gratefully acknowledged.

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