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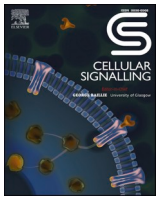

HIPK2 in cancer biology and therapy: Recent findings and future perspectives

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ABSTRACT

Homeodomain-interacting protein kinase 2 (HIPK2) is a serine-threonine kinase that phosphorylates and regulates a plethora of transcriptional regulators and chromatin modifiers. The heterogeneity of its interactome allows HIPK2 to modulate several cellular processes and signaling pathways, ultimately regulating cell fate and proliferation. Because of its p53-dependent pro-apoptotic activity and its downregulation in many tumor types, HIPK2 is traditionally considered a *bone fide* tumor suppressor gene. However, recent findings revealed that the role of HIPK2 in the pathogenesis of cancer is much more complex, ranging from tumor suppressive to oncogenic, strongly depending on the cellular context. Here, we review the very recent data emerged in the last years about the involvement of HIPK2 in cancer biology and therapy, highlighting the various alterations of this kinase (downregulation, upregulation, mutations and/or delocalization) in dependence on the cancer types. In addition, we discuss the recent advancement in the understanding the tumor suppressive and oncogenic functions of HIPK2, its role in establishing the response to cancer therapies, and its regulation by cancer-associated microRNAs. All these data strengthen the idea that HIPK2 is a key player in many types of cancer; therefore, it could represent an important prognostic marker, a factor to predict therapy response, and even a therapeutic target itself.

1. Introduction

1.1. HIPK2: a pleiotropic/multifunctional kinase

Homeodomain-interacting protein kinase 2 (HIPK2) is one of the four members (HIPK1, HIPK2, HIPK3, and HIPK4) of a family of serine-threonine kinases [1,2]. HIPKs were originally identified as corepressors of homeodomain-containing transcription factors, but they are able to phosphorylate and modulate the activity of many transcriptional regulators and chromatin modifiers [3]. Because of this wide spectrum of interactions, HIPKs play an important role in a multitude of cellular processes, as well as in embryonic development [4]. HIPKs act as transcriptional coregulators in important signal transduction pathways, such as Wnt/β-catenin, TGF-β, MAPK, Notch, Salvador–Warts–Hippo, and androgen receptor (AR), contributing to their cross-talk [5,6]. HIPK2 is the best characterized member of the family, and it is actively involved in the regulation of cell proliferation, apoptosis, DNA damage response, cytokinesis, transcription, and protein stability [7–13]. HIPK2 expression and activity are tightly regulated by post-translational modifications and microRNAs (miRNAs), and its functions strongly depend on the cellular context and on its subcellular localization, which can be nuclear and/or cytoplasmic [10–12].

The generation and phenotypic characterization of *Hipk2*-null (*Hipk2*-KO) mice demonstrated how this kinase is important for the physiological homeostasis of different tissues and organs *in vivo*. In fact, *Hipk2*-KO mice are significantly smaller than their wild-type littermates, and show several neuronal and cardiac defects [14], as well as skeletal muscle alterations. In particular, null-mice display morphological and psychomotor behavioral alterations due to a reduction in midbrain dopamine neuron survival, and to apoptosis of cerebellar Purkinje cells [15,16]. Interestingly, the appearance of even more dramatic phenotype may be prevented by the functional redundancy between HIPK2 and HIPK1. In fact, these two proteins are highly homologous and play overlapping roles in mediating cell proliferation and apoptosis in response to morphogenetic and genotoxic signals during mouse development. This is demonstrated by the embryonic lethality of their double KO as consequence of angiogenesis defects associated with hyperactivation of TGF-β signaling [17,18]. Recently, we reported that

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Hipk2-KO mice present neuronal loss, morphological alterations, and satellitosis throughout the whole central nervous system (CNS); a myopathic phenotype characterized by variable fiber size, mitochondrial proliferation, sarcoplasmic inclusions, morphological alterations at neuromuscular junction; and a cardiac phenotype characterized by fibrosis and cardiomyocyte hypertrophy [19]. Finally, the double KO of HIPK2 and High-Mobility Group A1 (HMGA1), a chromatin non-histone protein previously identified as HIPK2 interactor and substrate, causes perinatal death due to respiratory failure, associated with impaired lung development and reduction in surfactant proteins, as well as to reduced expression of thyroid differentiation markers [20], suggesting that HIPK2 is involved also in the development of endodermal-derived organs.

1.2. HIPK2 and cancer

Because of their important role in the regulation of cell proliferation, survival, and cancer-related signaling pathways, HIPK proteins have traditionally been linked to the pathogenesis of cancer and fibrosis, which are often associated with deregulated activity or expression of HIPKs [21]. In particular, because of its involvement in DNA damage repair and induction of apoptosis, HIPK2 is considered a *bona fide* tumor suppressor [6–12,21–24]. Indeed, HIPK2 expression is downregulated in different malignant tumors (Table 1), including breast, thyroid, and colon carcinomas [25,26]. However, HIPK2 downregulation often correlates with tumor progression and chemoresistance, and it can represent a prognostic marker for several cancer types. However, increasing evidence is showing that the role of HIPK2 in cancer cells is much more complicated than that of a canonical pro-apoptotic and DNA-repair factor, and it can even be oncogenic under specific circumstances.

The role of HIPK2 in cancer has been previously well reviewed [27,28]. Here, we will mainly focus on the data emerged in the very last years, pointing out the newly discovered tumor-suppressive and oncogenic functions of HIPK2, the functional relationship between HIPK2 and chemoresistance, and the miRNA-mediated HIPK2 regulation in cancer cells.

1.3. HIPK2 as a "typical" caretaker tumor-suppressor

On the basis of the first reports about its role in cancer cells, HIPK2 was considered a canonical "caretaker" gene, whose inactivation increases tumorigenicity [10], whereas its activation inhibits tumor growth [29]. Unquestionably, HIPK2 inhibits tumor growth through multiple mechanisms: promoting apoptosis, inhibiting angiogenesis, tumor invasion, and metastasis. These effects are achieved through the regulation of various genes and signaling pathways such as p53 [22,24], JNK [30],Wnt [31], and VEGF [32]. The activation of p53, through the phosphorylation of its Ser46, is the best characterized function of HIPK2, and, probably, the main mechanism through which it exerts its pro-apoptotic activity. In fact, when phosphorylated on Ser46 by HIPK2, p53 promptly activates the expression of pro-apoptotic genes, such as p53AIP1 [33], p21Waf1 [34], Noxa [35], Bax and Puma [36], and induces cell death. HIPK2-mediated p53 activation often occurs when HIPK2 is stabilized and activated as a response to DNA damage, and it triggers apoptotic cell death when DNA damage cannot be properly repaired [4]. Interestingly, human Papillomavirus E6 Protein (HPV23 E6), which is known for its oncogenic effects, inhibits HIPK2-mediated phosphorylation of p53 at Ser46 by disrupting HIPK2/p53 axis [37]. Moreover, HIPK2 can promote apoptosis also through other mechanisms: targeting p53-family members p63 and p73 [38], anti-apoptotic trans-repressor C-terminal binding protein (CtBP) [39,40], p53-inhibitor MDM2 [41], caspase-dependent processing [42] and the scaffold protein Axin [43].

Through the regulation of several different signaling pathways, HIPK2 can also regulate hypoxic response, angiogenesis, cell migration and metastatization. The effects of HIPK2 on hypoxic response depends on its ability to inhibit hypoxia inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF), two major tumorigenic factors that activate angiogenesis- and invasion-related genes [44]. Moreover, under hypoxia, HIPK2 itself is downregulated by hypoxia-induced ubiquitin ligases such as seven *in absentia* 2 (SIAH2), seven *in absentia* 1 (SIAH1) or Mouse Double Minute 2 homolog (MDM2), which can impair the HIPK2-mediated activation of cell death [45]. In fact, the degradation of HIPK2 can effectively inhibit chemo- and radio-therapy-induced p53 apoptotic activity, thus reducing therapy effect and promoting cancer progression [46–48]. The inhibition of Wnt/β-catenin signaling and the phosphorylation and degradation of the pro-metastatic protein CtBP1 account for HIPK2 ability to repress cellular invasion and tumor metastasis [40]. HIPK2 can also inhibit the activation of c-Myb [49], mitogen-activated protein kinase (MAPK), JNK and AKT pathways, which would promote cell proliferation, anchorage-independent growth and invasion [50].

Finally, HIPK2 has been reported to be involved in the maintenance

Table 1
HIPK2 status in different cancer types.

HIPK2 status		Cancer type	Effects
Downregulated		*Colorectal Cancer*	Pro-angiogenic effects through VEGF pathway activation [116]
		Osteosarcoma	Inhibition of apoptosis and resistance to chemotherapeutic drugs; lower patient survival [57,58]
		Gastric Cancer	Increased cell proliferation, viability and migration through miR-222-3p/HIPK2 axis [115]
		Hepatocellular Carcinoma	Enhanced migration, tumor growth angiogenesis through the HIF-1α pathway; worse survival [55]
		Pancreatic Cancer	Enhanced tumor proliferation and glycolysis through inhibition of ERK/cMyc axis; worse survival [59,112]
		Nasopharyngeal Carcinoma	Increased migration, invasion, and metastasis through SPEN/c-JUN/miR-4652-3p axis [113]
		Lung Adenocarcinoma	Activation of EMT and promotion of metastasis [114]
		Non-Small Cell Lung Cancer	Pro-angiogenic effect, increased tumor growth and metastatic potential [117]
Mutated	High mutation frequency	*Colorectal Cancer*	Poor prognosis [60]
	R868W N958I	*Acute Myeloid Leukemia*	HIPK2 PML-NBs delocalization, disruption of AML1-mediated activation of target genes for myeloid differentiation [84]
	Increased copy number	*Non-Small Cell Lung Cancer*	Enhanced tumor proliferation through YAP/TEAD pathway activation; lower patient survival [74]
Upregulated		*Tonsillar Squamous Cell Carcinomas*	Tumor progression through apoptosis inhibition; poor disease-free survival in human papillomavirus-positive carcinomas [86]
	CircHIPK2	*Ovarian Cancer*	DDP resistance and malignant behaviors through circHIPK2/miR-338-3p/CHTOP ceRNA regulatory axis [108]

of genomic integrity, another important function of caretaker genes. In fact, HIPK2 deficiency has been linked to chromosomal instability *via* cytokinesis failure, and increased tumorigenicity in mouse embryonic fibroblasts [10,51].

1.4. Not just a tumor-suppressor: the variegated role of HIPK2 in cancer cells

HIPK2 binds and regulates a plethora of transcription factors and cofactors and, therefore, it is not surprising that the effects of its activity are strongly dependent on the cellular context. Interacting with different proteins in different cell types and under different environmental and stress conditions, HIPK2 functions are diversified and heterogenous, and include the regulation of cellular survival, proliferation, and cell death [29]. Moreover, the activity of HIPK2 and its versatile binding ability make the scenario more variegated and strictly dependent on cellular context and environmental cues. Hence, the role of HIPK2 in cancer cells is characterized by noticeable variability, and it goes far beyond its "canonical" tumor-suppressive function of p53 activator and caretaker gene. In fact, HIPK2 can also have an oncogenic role in certain cancer types. Consistently, the expression levels of HIPK2 itself is different in different tumor types: it is usually downregulated in cell types in which it has tumor suppressive functions, and upregulated in cell types in which it has oncogenic functions [52–54].

Here, we report the most relevant recent findings about HIPK2 alterations and functions in different tumor types.

2. Recent discoveries about HIPK2 tumor suppressive functions

2.1. HIPK2 downregulation and mutations are associated to bad prognosis in colorectal cancer, osteosarcoma, and liver carcinoma

As we discussed before, several studies pointed out how HIPK2 exerts canonical tumor-suppressive functions in cancer cells, like induction of apoptosis, and inhibition of angiogenesis, cell migration and invasion, and how its expression can be very important for cancer biology and could have a potential relevance in clinical practice. In fact, HIPK2 loss or downregulation has been observed in many types of human tumors, including hepatocellular carcinoma (HCC) [55], colorectal cancer (CRC) [56], papillary and follicular thyroid carcinomas [26], osteosarcoma [57,58] and pancreatic cancer [59]; reduction of HIPK2 levels often correlates with cancer progression, and is associated with bad prognosis. The majority of the recent findings about the role of HIPK2 confirms its tumor-suppressive functions and the idea that it can represent an important prognostic marker for human cancers. For instance, the importance of HIPK2 in CRC was revealed by a study showing that HIPK2 sensitizes colon cancer cells to the treatment with the drug verbascoside, and that HIPK2 expression is downregulated in CRC samples, and inversely correlates with Dukes stage and depth of invasion [56]. Consistently with these findings, a recent whole-exome sequencing study performed on CRC samples and their liver metastasis shows that HIPK2 is one of the three genes with the highest mutation frequency, together with titin (TTN) and obscurin (OBSCN) [60]. Similarly, HIPK2 expression has emerged as a prognostic factor also for osteosarcoma patients survival. In fact, through a Weighted Gene Correlation Network Analysis (WGCNA), Li et al. identified HIPK2, together with MAP3K5 and CD54, as a key factor negatively correlated with survival risk in osteosarcoma patients [57]. HIPK2 is frequently downregulated also in HCC, which is the third leading cause of cancer deaths worldwide, and HIPK2 downregulation is associated with worse overall survival in HCC patients as well [55].

Taken together, these data strongly suggest that HIPK2 could be a reliable prognostic marker for CRC, HCC and osteosarcoma patients. Considering that similar observations had already been made for other cancer type [55,59,95–98], the prognostic usage of HIPK2 appears to be one of the most promising translational opportunities opened up by the studies about this kinase in cancer cells. However, large clinical trials that could demonstrate the concrete clinical relevance of these findings are still missing.

2.2. New targets and mechanisms through which HIPK2 exerts its tumor suppressive activity

As aforementioned, HIPK2 is often downregulated in HCC derived cells, and recent study unraveled the functions exerted by HIPK2 in this tumor type. Chen and colleagues reported that the restoration of HIPK2 expression inhibits the migration of Hep3B and CSQT-2 cell lines, as well as HCC tumor growth, angiogenesis and metastasis in mice [55]. Moreover, HIPK2 anti-angiogenic effect is due to its ability to bind HIF-1α, and to stimulate its ubiquitination and proteasomal degradation (Fig. 1A) [55].

In addition, HIPK2 negatively modulates the Wnt/β-catenin signaling pathway, which is often hyper-activated in HCC cells. In particular, HIPK2 can bind one of the main signal transducers of this pathway, Dishevelled-3 (Dvl3), and convert it into an unstable phosphorylated form, which is recognized by Itchy E3 ubiquitin protein ligase (ITCH), and addressed to proteasomal degradation. Dvl3 is overexpressed at protein level in human HCCs, and its overexpression promotes cancer cell stemness *via* the upregulation of Leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5), which further potentiates Wnt/β-catenin pathway activation. For these reasons, HIPK2-mediated DVL3 regulation can be crucial in the pathogenesis of HCC [61].

Evidence has emerged also about the role of HIPK2 in pancreatic and prostatic cancer cells. In pancreatic cancer, the HIPK2 tumor suppressive role is exerted *via* the inhibition of ERK which would, in turn, activate and stabilize the oncogenic protein c-Myc, which can promote cell proliferation by increasing aerobic glycolytic activity. The overexpression of HIPK2 prevents this effect, attenuating c-Myc activation, thus decreasing aerobic glycolysis and proliferation of Panc-1 and SW1990 pancreatic cancer cells [59]. Consistently, decreased HIPK2 expression is associated with a negative prognosis of pancreatic cancer patients [59].

In prostate cells, upon DNA damage, HIPK2 promotes the activation of DNA repair pathways. In particular, HIPK2 phosphorylates heterochromatin protein 1 (HP1), thus disrupting its association with trimethylated (Lys9) histone H3 (H3K9me3), that would inhibit DNA repair initiation [62]. Interestingly, HIPK2 ability to phosphorylate HP1 depends on a specific non-degradative HIPK2 ubiquitination, which is induced by Speckle-type Poz Protein (SPOP), an E3 ubiquitin ligase adaptor, the most frequently mutated gene in prostate cancer [63]. The effect of SPOP on the HIPK2-HP1 axis is abrogated by prostate cancer-associated SPOP mutations, thus representing a new mechanism of SPOP mutations-driven genomic instability in prostate cancer [64].

Other recently emerged HIPK2 tumor suppressive functions include its involvement in the processes of cytokines, inflammation and tumor microenvironment establishment [65–67]. One of the main HIPK2 tumor-suppressive function is to contribute to the maintenance of genome stability, by facilitating a successful cytokinesis process. During cytokinesis, HIPK2 localizes at the midbody, a transient electron-dense structure that works as a platform for the spatial-temporal distribution of specific proteins and lipids that contribute to cellular abscission [68]. In particular, the HIPK2-mediated phosphorylation of the extrachromosomal histone H2B [51,69] and of the microtubule severing enzyme Spastin [70,71] contribute to the formation of the abscission site, and to the separation of the two daughter cells. Cytokinesis defects are a common feature of cancer and lead to the accumulation of multiploidy cells. Recently, emerging evidence indicated that the midbody remnant (MBR), the residual part of the midbody that persists after abscission, can act as a post-abscission signaling platform, and that aberrant MBR accumulation often occurs in cancer cells, where it seems able to promote cell stemness, proliferation, and tumorigenicity. After abscission,

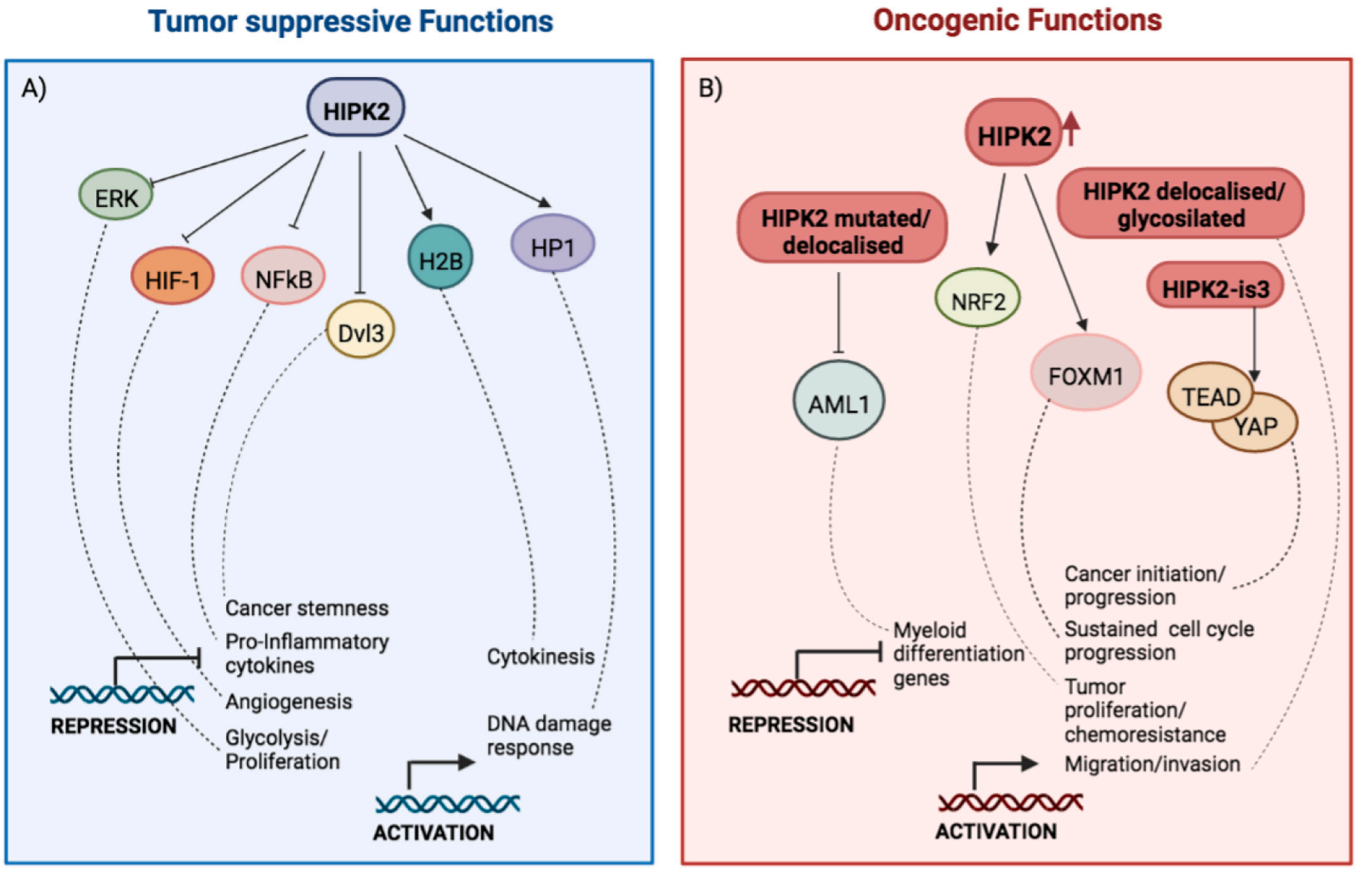

Fig. 1. Tumor suppressive and oncogenic functions of HIPK2.
Schematic representation of the tumor suppressive (A) and oncogenic (B) effects caused by the functional interactions between HIPK2 and its recently identified targets/molecular partners.

the MBR can be retained, released, internalized by nearby cells, or removed through autophagy-mediated degradation, a process in which HIPK2 has recently been reported to be involved. In fact, HIPK2 depletion leads to significant accumulation of MBRs, associated with an accumulation of CEP55, a key effector of both midbody formation and MBR degradation, and to an impairment of the autophagic flux [67].

HIPK2 exerts also an "anti-inflammatory" effect by inhibiting NF-κB activation in macrophages (Fig. 1A). In particular, HIPK2 phosphorylates HDAC3 disabling its deacetylase activity, and this inhibition results in the increase of K218 acetylation of the p65 subunit of NF-κB [65]. Acetylated p65 suppresses NF-κB activation and inhibits the production of pro-inflammatory cytokines. This effect could be particularly relevant for the pathogenesis of cancer types that are strongly promoted by sustained inflammation like CRC, in which, as abovementioned, HIPK2 is often found mutated or downregulated. Consistently, *Hipk2*-deficient mice are susceptible to LPS-induced endotoxemia, and adoptive transfer of *Hipk2*$^{+/-}$ bone marrow cells also aggravated Azoxymethane (AOM)/ Dextran Sodium Sulfate (DSS)-induced tumors in mouse model of inflammatory CRC [58]. This last observation demonstrates how mouse models can be a precious tool for *in vivo* validation of the findings about the role of HIPK2 in cancer cells obtained *in vitro*. So far, one study has reported that *Hipk2*-KO mice are more susceptible to skin chemical carcinogenesis than their wild-type counterpart [11]. Interestingly, heterozygous loss of HIPK2 leads to lymphoma development upon γ-radiation [72], supporting the idea that HIPK2 can behave as an haploinsufficient tumor suppressor in this cancer context. On the same line, a study based on a human tissue microarray revealed an inverse correlation between HIPK2 levels and DNA ploidy in pancreas carcinogenesis [10], thus pointing out HIPK2 as a care-taker gene. Altogether these findings support a gene-dosage effect of *HIPK2* in cancer. One can envisage that the absence and/or very low dosage of HIPK2 may concur to carcinogenesis by accelerating tumor progression. It would be useful to study if and how ubiquitous or organ-specific *Hipk2* gene deletions affect cancer initiation and progression in mouse models of chemical- or genetic-induced carcinogenesis for a better understanding of the functional link between HIPK2 and cancer. Hence, other studies comparing the behavior of *Hipk2*$^{-/-}$ and *Hipk2*$^{+/-}$ mice will be important to better clarify the gene-dosage effects of *Hipk2,* and well define it as a marker for early detection of neoplastic lesions. Similarly, a better understanding of the molecular mechanisms responsible for the role of HIPK2 in carcinogenesis and for its dosage effect could be achieved using valuable experimental models whose usage is still missing in the field, like organoid cultures and/or patient-derived xenograft.

Finally, lack of HIPK2 expression may be important also for the establish of tumor microenvironment. In fact, it has been shown that culturing human fibroblasts with conditioned media derived from cancer cells, where HIPK2 expression is suppressed, induces a trans-differentiation process which confers them the molecular feature of cancer-associated fibroblasts (CAFs), including expression of α-smooth muscle actin (α-SMA) and collagen I, and autophagy–mediated caveolin-1 degradation [66]. CAFs are known to sustain cancer growth and survival and support malignancy and tumor resistance to therapies [66]. Interestingly, many clinical studies documented how CAF abundance and function are linked to tumor outcome, suggesting that targeting CAFs could represent a powerful addition to canonical anticancer therapies. Many approaches are being tested to target CAFs, including the modulation of TGFβ signaling, MAPK, and fibroblast activation protein (FAP) [73]. Even if these data about the functional relationship between

HIPK2 and tumor microenvironment are somehow preliminary, they open up very interesting opportunities for the field. It would be interesting to evaluate *in vivo* whether the restoration of HIPK2 expression and function can induce CAFs re-conversion into "normal" fibroblasts, and thus improve the tumor outcome.

3. Recent discoveries about HIPK2 oncogenic functions

Even if most of the data about HIPK2 role in human tumors indicates that it exerts a tumor suppressive function (Table 1), several reports unraveled an opposite behavior of HIPK2 in other types of cancer, and highlighted the mechanisms by which HIPK2 may exert an oncogenic role (Fig. 1B). In particular, HIPK2 is frequently amplified and overexpressed in pilocytic astrocytoma [52], and its expression is significantly higher in cervical cancer than in healthy tissue [53]. In addition, HIPK2 expression is also significantly higher in aggressive meningiomas than in benign ones [54].

Recently, a new HIPK2 isoform (containing exons 1-13a and 13b) was discovered in non-small cell lung cancer (NSCLC) H1975, A549, H1299, H460, H2030, and H2170 cell lines [74]. This isoform, called isoform 3 (HIPK2-is3), lacks exons 14 and 15 that encode for the C-terminal portion of the main HIPK2 isoform (isoform 1, containing exons 1-13a, 14 and 15). Interestingly, NSCLC cell lines display increased HIPK2 DNA copy number and NSCLC samples display selective overexpression of HIPK2-is3. HIPK2-is3 promotes the activation of the Hippo pathway, which is one of the key drivers of lung cancer initiation and progression [75]. In particular, HIPK2-is3 increases, in a kinase-dependent manner, TEAD activity (a typical read-out of Hippo pathway activation), and YAP protein stability in NSCLC. Together with the observation that high HIPK2 mRNA expression in the Human Protein Atlas platform negatively correlates with NSCLC patient survival, these data suggest that HIPK2-is3 plays an oncogenic role in NSCLC [74]. Interestingly, HIPK2 is transcriptionally regulated by nuclear factor erythroid 2 (NF-E2) p45-related factor 2 (NRF2) in H1299 and A549 NSCLC cell lines [76]. NRF2 is a transcriptional factor that is considered the master regulator of oxidative stress response because of its ability to allow adaptation and survival under stress conditions, *via* the regulation of a wide set of genes coding for anti-oxidant and drug-metabolizing enzymes, and for drug transporters [77,78]. Recently, it has been shown that the functional interaction between HIPK2 and NRF2 takes place at two different levels. On one hand, NRF2 regulates HIPK2 expression at transcriptional level; on the other hand, HIPK2 is required for NRF2 activity, contributing to induce the expression of NRF2 targets, and to elicit a cytoprotective response, which has an ambivalent role in cancer development. In fact, while a transient NRF2 activation is linked to chemoprevention, its sustained activity favors tumor cell resistance to chemo- and radiotherapy, and can support cell proliferation and tumor growth [79,80]. Consistently, NRF2 is often constitutively activated in human tumors [81,82], and it is associated with poor prognosis. For these reasons, sustaining prolonged NRF2 activity could be a potential oncogenic function exerted by HIPK2 under specific conditions [76].

An example of how HIPK2 can have an oncogenic role *per se* has been provided by the study of HIPK2 dominant negative mutations (R868W and N958I) that are found in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) patients [83]. Under physiological conditions, HIPK2 is part of the promyelocytic leukemia protein-nuclear bodies (PML-NB), sub-nuclear structures that are crucial for the expression of myeloid differentiation genes, whose formation and activity is impaired in AML and MDS [83]. Interestingly, R868W and N958I HIPK2 mutations disrupt HIPK2 SUMO-interacting motif (SIM), impairing HIPK2 SUMOylation. The lack of this post-translational modification prevents HIPK2 localization in the PML-NB, but not its ability to bind and phosphorylate AML1b protein [83]. For these reasons, HIPK2 mutants can sequestrate the AML1 complex out of the PML-NBs, thus disrupting the AML1-mediated activation of myeloid differentiation genes [83,84].

Even in the absence of consistent mechanistical explanations, Kwon et al. have suggested a potential oncogenic role for HIPK2 in tonsillar squamous cell carcinomas (TSCCs), the most common human papillomavirus (HPV) - associated oropharyngeal cancers with poor prognosis [85]. HIPK2 has been found to be associated with the oncogenic HPV protein E6, known to induce the proteolytic degradation of p53, and of other important pro-apoptotic proteins, like Bak and Bax. Moreover, HIPK2 mRNA expression is higher in TSCCs than in normal tonsils, and its overexpression is associated with poorly differentiated carcinoma, representing also an independent negative prognostic factor for overall survival and disease-free survival (DFS) of HPV-positive TSCCs. The correlation between HIPK2 overexpression and poor prognosis and survival suggests that HIPK2 may have an oncogenic role also in TSCCs [86]. Similarly, a HIPK2 mRNA and protein expression analysis performed in oral squamous cell carcinoma (OSCC) samples and their lymph node metastasis revealed that HIPK2 nuclear delocalization occurs during oral epithelial cancer progression, and it is associated with cervical lymph node metastasis and poor outcome. The role of HIPK2 in oral epithelial cells has been defined by *in vitro* experiments, showing that HIPK2 normally prevents epithelial-mesenchymal transition (EMT) and cell invasion by inhibiting E-cadherin expression in a p53-dependent manner [85]. However, HIPK2 has been found to be delocalized in OSCC, and this delocalization can impair its EMT inhibiting activity, thus increasing the migration and invasion potential of oral squamous cells [85]. Further studied are needed to establish the mechanisms of HIPK2 nuclear delocalization to cytoplasmic relocalization, and to clarify whether this delocalization has an active oncogenic role in OSCC or simply impairs the physiological "protective" functions of the kinase.

Another cancer type in which the role of HIPK2 has recently been highlighted is renal cell carcinoma (RCC), a common malignant tumor which is often metastatic and poorly responsive to cancer therapy. In particular, Liu et al. reported that HIPK2 binds and phosphorylates Forkhead Box M1 (FOXM1) on Ser724 [87], a transcription factor which regulates G1-S and G2-M cell cycle transitions and the maintenance of mitotic spindle integrity [88,89], whose expression is increased in renal cell carcinoma (RCC) samples. Interestingly, HIPK2 knock-down inhibits FOXM1 phosphorylation and reduces transcription of FOXM1-target genes, such as *CCNB1* (Cyclin B1) and *AURKB* (Aurora B), thus impairing cell cycle progression and reducing cell viability [87]. These data suggest that HIPK2 may promote FOXM1 oncogenic activity in RCC. Finally, some preliminary data suggest that glycosylation may confer pro-proliferative oncogenic functions to HIPK2. HIPK2 is glycosylated at S852, T1009 and S1147 by O-GlcNAc transferase (OGT) and this glycosylation increases HIPK2 protein stability, preventing its proteasomal degradation [87]. OGT is involved in cancer biology, and its expression is upregulated in different cancer types, and is also associated with poor prognosis of patients with prostate or breast cancers [90,91], aggressiveness of bladder tumors [92], and tumor recurrence of liver cancer [93]. Interestingly, the OGT-mediated HIPK2 stabilization sustains an abnormal tumor-like cell proliferation in Drosophila, suggesting that OGT may affect HIPK2 stability and activity also in human cancer cells [87].

It is important to point out that, while HIPK2 expression levels and mutational status have been evaluated in a multitude of different cancer samples, their intra-tumor heterogeneity has not been exhaustively investigated yet. In this perspective, the field could benefit from single-cell analysis of HIPK2 expression levels and mutational status, to evaluate whether HIPK2 alterations are more frequent in specific cancer subpopulations (*e.g.*, in cancer stem cells). Moreover, as for HIPK2 tumor suppressive functions, also the evaluation of its oncogenic features may benefit from *in vivo* studies performed in mouse models, and *in vitro* experiments performed using organoid cultures and patient-derived xenografts. In particular, the generation and characterization of transgenic mice overexpressing HIPK2 might show whether higher level of this kinase are sufficient to induce cancer formation *per se,* and/or to

increase the susceptibility to chemical- or genetic-induced cancer in specific organs and tissues, like cervix or lung.

4. HIPK2 and chemoresistance

Because of HIPK2 ability to regulate cell survival, its activity and expression levels have been found to be related to chemoresistance in several cancer types. Unsurprisingly, the most important HIPK2 function that mediates the cytotoxic effect of several chemotherapeutic agents is its p53-dependent pro-apoptotic activity. Interestingly, HIPK2 itself is activated by various anti-cancer drugs, including cisplatin (CDDP), adriamycin (ADR) and roscovitin [27], and this activation triggers the HIPK2/p53Ser46 apoptotic signaling pathway, whose deregulation is often observed in chemoresistant cells [27]. HIPK2 has been related to chemoresistance also for its ability to sensitize cancer cells to therapy by inhibiting the wild-type p53-induced phosphatase 1 (Wip1) [94] or HIF-1α [32], or by targeting ΔNp63α in p53-null cells [95]. Recently, additional evidence of the importance of this kinase in cancer therapy has emerged (Fig. 2).

Indeed, Wang et al. showed how the HIPK2/p53-dependent apoptotic pathway mediates the effect of 4-hydroxybenzoic acids (4-HBA) 13a, a new HDAC6 inhibitor, which is able to reduce the resistance of breast cancer cells to adriamycin (ADM) [96]. 4-HBAs-13a potentiates ADM-induced apoptosis by enhancing p53 and HIPK2 expression in ADM-resistant breast cancer cells. Consistently, the apoptosis induced by the co-treatment with 4-HBAs-13a and ADM strongly diminishes upon HIPK2 knock-down [96]. Similarly, He et al. provided evidence that HIPK2 and its negative regulatory E3-ubiquitin ligase SIAH are critical factors controlling temozolomide-induced cell death in glioblastoma LN-229 and glioma U87MG cell lines. In fact, upon temozolomide treatment, the O6MeG carcinogenic DNA lesion triggers HIPK2 stabilization probably due to DNA-damage induced disruption of the HIPK2–Siah-1 complex [38,97,98], thus resulting in kinase activation, p53Ser46 phosphorylation, and stimulation of the pro-apoptotic FAS pathway. Moreover, downregulation of SIAH1, which is significantly overexpressed in glioblastomas, ameliorates temozolomide-induced apoptosis, suggesting that HIPK2 plays a relevant protective pro-apoptotic role in glioblastoma LN-229 cells, even in the absence of a chemotherapeutic treatment [99].

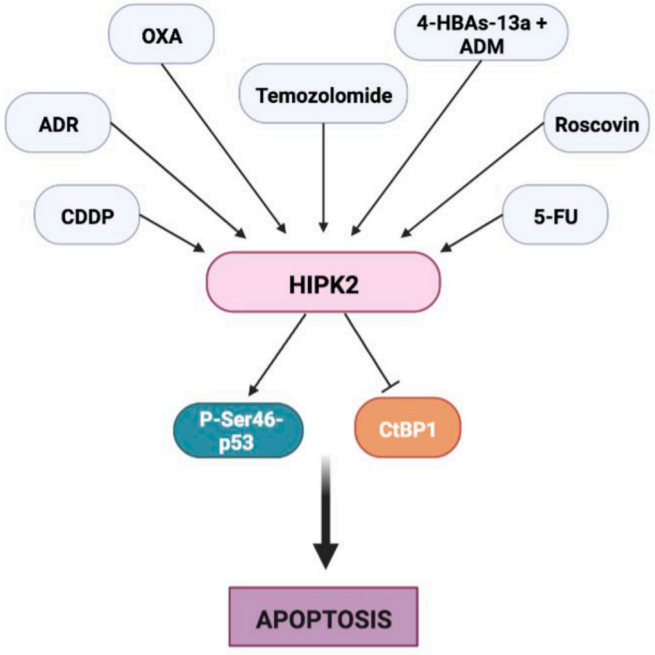

Fig. 2. Crosstalk among chemotherapeutics, HIPK2 and cancer treatment. Schematic representation of the chemotherapeutic agents able to exert their cytotoxic activity *via* HIPK2.

The canonical p53-mediated pro-apoptotic effect is not the only way by which HIPK2 may influence cancer cell survival and response to therapeutic agents. The functional interaction between HIPK2 and NRF2 may be another key factor in these regards. In fact, as we discussed before, the complex interplay between HIPK2 and NRF2 may be an oncogenic pro-survival effect under specific circumstances. According to a recent study [100], upon specific metabolic conditions *i.e.*, hyperglicemia in diabetes and obesity cancer patients, the NRF2/HIPK2/p53 interplay may have a pro-survival effect allowing cancer cells to bypass drug cytotoxicity. For example, HIPK2 and NRF2 expression has been associated with chemoresponse in early stage CRC [100]. In particular, the NRF2 inhibitor brusatol induced an increase in chemotherapy response only when HIPK2 is expressed, confirming that HIPK2 is a crucial factor for therapies based on NRF2 modulators [101]. Moreover, the importance of HIPK2 in CRC therapy is confirmed by the fact that HIPK2-KO induces resistance to Fluorouracil (5-FU) and oxaliplatin (OXA), two drugs frequently used in the treatment of CRC [101,102].

Another HIPK2 molecular partner that is involved in chemoresistance is the transcriptional corepressor CtBP1, which is able to inhibit the expression of several tumor-suppressor genes. Interestingly, its functional interaction with HIPK2 has been reported to be important to determine the response of osteosarcoma cells to chemotherapy. In fact, the assembly of CtBP1-p300-FOXO3a transcriptional complex represses the expression of pro-apoptotic genes such as Bax and Bim in osteosarcoma cells [58]. As we mentioned before, HIPK2 is able to inhibit CtBP1 by phosphorylating it and promoting its proteosomal degradation [103]. Duan et al. found a significant decrease in the expression levels of HIPK2 and phosphorylated CtBP1 in osteosarcoma cells and biopsies, associated with an increase in CtBP1 expression level. Moreover, overexpression of HIPK2 disrupts the CtBP1-mediated transrepression of pro-apoptotic genes, and results in induction of apoptosis and increased chemosensitivity of osteosarcoma cells [58].

Interestingly, even a SNP within the HIPK2 gene has been associated with a specific response to cancer therapy. In fact, HIPK2 SNP rs2030712 has been found to be significantly associated with the occurrence of radiation pneumonitis in patients with pulmonary malignancies treated with radiotherapy [104]. Finally, the expression of a HIPK2 circular RNA (circHIPK2) has been found to be associated with cisplatin (DDP) chemoresistance in ovarian cancer (OvCa) samples. Circular RNAs (CircRNAs) are covalently closed long non-coding RNAs that exert crucial biological functions in human diseases with tissue-specific and cell-specific patterns [105]. CircRNAs regulate gene expression by acting as miRNA sponges, RNA-binding protein sequestering agents, or nuclear transcriptional regulators. Many circRNAs have been found to be upregulated during mouse neural development and human epithelial-mesenchymal transition, and are aberrantly expressed in several vascular diseases, neurological disorders, and cancers [106]. The expression, function and mechanism of circRNAs have been systematically over-viewed in gynecological cancers including OvCa [107]. In these tumors, circHIPK2 knock-down suppresses DDP resistance. Moreover, cell proliferation, cell cycle regression, migration and invasion, as well as tumor growth of OvCa cells, are overall restrained by silencing circHIPK2, suggesting an anti-tumor role of circHIPK2 knock-down in DDP-resistant OvCa SKOV3/DDP and A2780/DDP cells both *in vitro* and *in vivo* [108].

Taken together, these data support the idea that HIPK2 is important to establish an efficient response to several cancer treatments. Considering that The Cancer Genome Atlas (TCGA) consortium has made available big data sets correlating gene expression levels and mutational status to clinical outcomes and chemotherapy response [109–111], a metanalysis of the status of HIPK2 in these data sets could provide more solid evidence of the translational relevance of HIPK2 in the response to cancer therapy and in clinical practice.

5. HIPK2 and miRNAs functional interaction in cancer cells

As reviewed in [8,9], HIPK2 expression is regulated by several miRNAs, which are able to bind the 3'-UTR of *HIPK2* transcripts and to inhibit their translation. Over the last few years, new HIPK2-regulating miRNAs have been identified in different types of cancer cells (Table 2). In particular, four "onco-miR", miR-222-3p, miR-4652-3p, miR-197, and miR-222-3p, whose expression is increased in tumor cells with respect to their normal counterparts, have been shown to exert their oncogenic activity by downregulating HIPK2 expression, thus preventing the kinase from exerting its tumor suppressive functions.

miR-222-3p is significantly upregulated in pancreatic cancer tissues, in which it enhances glycolysis and promotes cell proliferation [112]. As we discussed before, these same effects had already been reported to be associated with the downregulation of HIPK2 increasing the ERK/c-Myc axis in Panc-1, SW1990 and primary pancreatic cancer cells [59]. Indeed, analyzing a cohort of pancreatic patient samples from The Cancer Genome Atlas (TCGA) database and Panc-1 and Mia-PaCa2 pancreatic cancer cell lines, Zhai and colleagues revealed an inverse correlation between miR-222-3p and HIPK2 expression. Moreover, the HIPK2/miR-222-3p functional interaction involves also the tumor suppressor long noncoding RNA (lncRNA) LINC00261, which can act as a "sponge" binding miR-222-3p, thus preventing its binding to HIPK2 mRNA. It has been shown that this "protective effect" of LINC00261 on miR-222-3p-induced HIPK2 downregulation can attenuate aerobic glycolysis in Panc-1 and Mia-PaCa2 pancreatic cancer cells [112].

Another HIPK2-regulator onco-miR is miR-4652-3p, which is upregulated *via* the PI3K/AKT/c-JUN signaling pathway in nasopharyngeal carcinoma NPC-HONE1 and immortalized nasopharyngeal NP69 cells. The main oncogenic effect of this miR is the activation of EMT signaling through which it promotes NPC migration, invasion, and metastasis [113]. EMT activation is the mechanism by which also miR-197 exerts its oncogenic activity. The expression of this miR has been correlated with lung adenocarcinoma (LAD) progression, and it has been shown that it strongly activates EMT and promotes LAD metastasis by directly silencing HIPK2 [114].

Similarly, HIPK2 expression is negatively regulated by miR-222-3p which is highly expressed in gastric cancer, especially in the *H. pylori* induced one. In particular, miR-222-3p-induced HIPK2 downregulation is associated with an increased in cell proliferation, viability and migration in SGC-7901 gastric cancer cells [115].

Recently, two circulating exosomal microRNAs (exomiRs) exomiR-1229 and exomiR-1260b have been reported to target and downregulate HIPK2 expression in colon and lung cancer cells respectively [116,117]. ExomiRs are miRNAs which are contained into exosomes, a type of extracellular vesicles that can be secreted by most cells, including tumor ones. Increasing evidence is showing that tumor-derived exosomes "indoctrinate" surrounding cells and modulate the microenvironment to facilitate tumor progression [118]. Specific exomiRs are found to be significantly increased in the serum of patients with specific cancer types [119], representing potential new diagnostic and prognostic markers for these neoplasias [120–122]. In colon cells, HIPK2 expression is inhibited by exomiR-1229, an exomiR targeting HIPK2 mRNA is upregulated in the serum of CRC patients [116]. Interestingly, exomiR-1229 overexpression correlates with tumor size, lymphatic metastasis, TNM stage and poor survival, and its oncogenic effects seem to be mainly due to its ability to down-regulate HIPK2 protein expression. In fact, exomiR-1229-induced HIPK2 downregulation potentiates VEGF pathway activation with consequent pro-angiogenic effects [116]. A very similar behavior is shown by exomiR-1260b, which is upregulated in non-small-cell lung cancer (NSCLC) patients [117]. ExomiR-1260b upregulation positively correlates with high-grade disease, metastasis, and poor survival of NSCLC patients, while it negatively correlates with HIPK2 expression. Also in this case, the miR-induced HIPK2 downregulation results in a pro-angiogenic effect that increases the tumor growth and metastatic potential [117].

Table 2
Newly discovered HIPK2-targeting miRs.

HIPK2-targeting miR	Cancer type	Effects
miR-222-3p	*Pancreatic Cancer*	Enhanced glycolysis and cell proliferation [112]
miR-4652-3p	*Nasopharyngeal Carcinoma*	EMT; metastasis [113]
miR-197	*Lung Adenocarcinoma*	EMT; metastasis [114]
miR-222-3p	*Gastric Cancer*	Enhanced cell proliferation, viability and migration [115]
exomiR-1229	*Colorectal Cancer*	Increased angiogenesis; high grade disease; metastasis [116]
exomiR-1260b	*Non-Small-Cell Lung Cancer*	Increased angiogenesis; high grade disease; metastasis [117]

All these reports clearly indicate that several onco-miRs exert their oncogenic activity by targeting HIPK2 in different cancer types. These observations suggest that "antagomiRs", small synthetic RNA that are perfectly complementary to specific target miRNAs, could be used to neutralize these HIPK2-targeting miRs, in order to restore physiological HIPK2 expression [121] and ameliorate the outcome of tumors like pancreatic, gastric and nasopharyngeal carcinomas.

6. Conclusions and future perspectives

In the last few years, many reports confirmed the importance of HIPK2 in cancer biology and therapy, and provided new insights on the cellular pathways in which this kinase is involved and the molecular mechanisms through which HIPK2 exerts its tumor suppressive/oncogenic role. Consistently with the heterogeneity of its activity, HIPK2 has been reported to be downregulated in CRC, HCC, osteosarcoma, and pancreatic cancer, whereas it is mutated, upregulated or delocalized in NSCLC, AML, TSCC, OSCC and RCC (Table 1). In the tumors in which HIPK2 is downregulated, it exerts a tumor suppressive activity, and its downregulation is associated with poor prognosis and low survival. As previously observed in other cancer types, the regulation of cell proliferation, migration and DNA repair, and the inhibition of oncogenic players, like HIF-1α, Wnt/β-catenin, MAPK, and c-Myc, are the main mechanisms through which HIPK2 plays its tumor suppressive role. In addition, new tumor suppressive mechanisms have been described, including the promotion of MBR degradation, the regulation of macrophage inflammatory activity, and the modulation of tumor microenvironment. On the other hand, HIPK2 has a direct or indirect oncogenic role in the tumors in which it is mutated, upregulated or delocalized, and, also in this case, its mutational or expression status has a prognostic value. Interestingly, HIPK2 has been shown to affect the responsiveness to cancer therapy of glioblastoma, osteosarcoma, colon and breast cancer cells, and to be the main effector through which several onco- and exomiRs exert their oncogenic activity in colon, lung, pancreas, stomach and nasopharyngeal cancers (Table 2).

Taken together, these data strengthen the idea that HIPK2 can be an important prognostic marker in a vast array of cancer types, an important factor to predict cancer therapy response, and a therapeutic target itself. In fact, depending on the cellular context, HIPK2 could be targeted to restore its tumor-suppressive functions to sensitize cancer cells to chemo- or radiotherapy, or to abrogate its oncogenic activity. Intriguingly, HIPK2 could be targeted directly or through the miRs that regulate its expression, which appear to be crucial for the role of HIPK2 in many cancer cells. In particular, depending on the cellular context, currently available HIPK2-selective inhibitors blocking its kinase activity [123,124], and/or "antagomiRs" binding/neutralizing HIPK2-targeting miRs [125], may represent potential promising therapeutics to be used in the near future.

It is important to highlight that, while the data reviewed here demonstrate that the role of HIPK2 in cancer biology is even deeper and more heterogenous than expected, the field would now need to adopt

new experimental approaches to reach the "next level" in understating, and, ideally, using the translational potential of this kinase. In fact, even if most of the recent reports provide interesting examples of new targets, mechanisms of action, mutations, and expression alterations of HIPK2, they are limited by the scarcity of *in vivo* experiments and analysis of conspicuous groups of patients. Hence, the next challenge is to increase pre-clinical studies in animal models to definitively clarify and envisage the modulation of HIPK2 expression and/or activity as potential treatment for cancer. This will realistically open the route for clinical studies. On the other hand, clinical studies on large cohorts of patients will be fundamental to unquestionably include HIPK2 as a prognostic marker in clinical practice.

Data availability

In this review article, the authors do not report any original data.

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