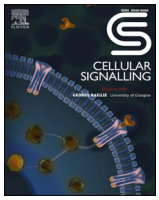
Cellular Signalling 93 (2022) 110303

Contents lists available at ScienceDirect

Cellular Signalling

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



Roles and regulation of Haspin kinase and its impact on carcinogenesis

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ARTICLE INFO

Keywords:
Haspin
Kinase
cancer
Genome stability
Primary cilia
Polarization

ABSTRACT

Cancer therapy is based on the selective clearance of malignant cells without severely damaging healthy tissues, and current clinical practice is constantly in need for new therapeutic targets in tumor management. The atypical protein kinase Haspin is conserved among most eukaryotes, and it has been shown to be particularly active in cycling cells. Along the years, several reports ascribed this protein the role to monitor chromosomal dynamics, primary cilia regulation and cellular polarization. Recently, an increasing amount of literature has depicted Haspin as a promising target to tackle tumors, as highlighted by its overexpression in malignant tissues and its requirement for cancer cell proliferation. In this work, we provide a detailed description on the current knowledge on Haspin, its physiological roles, the mechanisms underlying its regulation and its potential contribution to carcinogenesis.

1. Structure and regulation of Haspin kinase

The atypical protein kinase Haspin (Haploid germ cell-specific nuclear protein kinase) was originally identified in murine testis in 1999 [1], and was later found to be coded by an intron-less gene with transposon-like features located within an intron of integrin αE [2,3], named GSG2. Haspin paralogues have been found in most eukaryotes investigated so far [4–6], suggesting a conserved, prominent role in eukaryotic organisms. An initial characterization of Haspin sequence revealed a moderate conservation through evolution, with 66% of overall identity between the murine and human paralogues, which rises to 83% in the C-terminus [2,4], and a similar pattern of conservation in the C-terminus has been observed in other eukaryotes [7].

Under a structural point of view, Haspin kinase domain shows poor sequence homology with eukaryotic protein kinases (ePKs), bearing several peculiar inserts [7,8] including an atypical activation segment that specifically recognizes the basic histone tail. Moreover, Haspin lacks typical elements of ePKs such as the Asp-Phe-Gly ATP/Mg2+ binding motif, which is replaced by Asp-Tyr-Thr, and the presence of an Ala-Pro-Glu motif at the end of the activation segment [8]. Although expressed throughout the cell-cycle, Haspin activity peaks at mitosis [6] and is regulated by the presence of an autoinhibitory loop which folds on the catalytic domain. Multiple phosphorylation events by Cdk1 and Polo-like kinase in M remove the autoinhibition releasing the intrinsically active kinase activity [9,10].

Haspin localization, mainly studied by overexpression experiments, revealed it as a nuclear protein [11,12]. When cells enter mitosis, Haspin associates with condensing chromosomes, with a higher concentration in the centromeric region [11,13]. In prometaphase, it shows up at the centrosomes and in telophase at the midbody [11]. Unscheduled activity of Haspin is also prevented by modulating its localization, as a robust recruitment of this kinase to the chromatin only occurs following interaction with SUMOylated Topoisomerase IIα [14,15]. Still, basal levels of Haspin activity have been reported both in interphase cells, by Fresán et al. [16], and in quiescent cells, by us [17], thus suggesting the existence of other mechanisms subtly modulating Haspin activity out of mitosis.

2. Evidence for a pro-tumorigenic role for Haspin

As a central modulator of cell proliferation and chromosome segregation, Haspin is well positioned to be implicated in cancer. Multiple lines of evidence, recapitulated in Table 1, suggest that Haspin might indeed play a relevant role in tumorigenesis. Haspin was shown to be overexpressed in several transformed cell types compared to healthy counterparts, ranging from models of skin, lung, colon and bone cancers [18,19], to primary malignancies of the pancreas [20], gallbladder [21], prostate [22], bladder [23], ovaries [24], breast [25] and cholangiocarcinoma [26]. A direct correlation between Haspin expression levels and the grade of the malignancy [20–24,26] and an anti-correlation with patients' survival were reported [20,23,24,27]. Remarkably, this paradigm has been questioned by the observation that,

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https://doi.org/10.1016/j.cellsig.2022.110303
Received 8 February 2022; Received in revised form 4 March 2022; Accepted 4 March 2022
Available online 10 March 2022

in several breast cancer cell lines, Haspin expression levels do not correlate with malignancy grade but rather with the proliferative rate of the cells [28]. Up to now no efforts have been made to discriminate whether increased Haspin expression is ascribable to a faster proliferation or to peculiar tumor-specific pathways; yet, this upregulation is likely not due to an amplification of the GSG2 gene, as GSG2 loss of heterozygosity is often observed in cancers [8,29], and no differences in Haspin expression levels were observed in breast tumors with a deletion of one GSG2 allele compared to diploid counterparts [25].

Whatever the case, along the years several studies have shown an intimate connection between Haspin activity and tumor development. The first finding proposing Haspin as a target for cancer treatment came from Huertas and colleagues, who showed how treatment with Haspin inhibitor CHR-6494 led to mitotic catastrophe and apoptosis in breast, colon and ovary tumor models [30]. This concept was then extended by a plethora of studies conducted exploiting different chemical and silencing approaches to deprive the cells of Haspin activity in several cellular models: CHR-6494 was shown to trigger apoptosis in multiple melanoma cell lines [31] and decreased polyp formation in a familial colorectal cancer murine model [32], coumestrol has been reported to inhibit growth of melanoma, lung and colon tumoral models [18], 3*H*-pyrazolo[4,3-*f*]quinoline reduces growth of malignant colon, skin and cervix cell lines [33], and, more in general, loss of Haspin activity has been reported to cause an accumulation of G2/M cells and enhanced apoptosis in gallbladder [21], prostate [20,22,27], bladder [23], ovarian [24], skin [34] and breast [28] cancer models. In agreement with this, and supporting its requirement for carcinogenesis, loss of Haspin activity results in delayed tumor growth in multiple models of mouse xenograft [20–23,26,27,30,34]. On top of this, Haspin activity has been shown to sustain cellular migration in several cellular models [20,26,27,31]. Though we are still missing a clear mechanism by which Haspin contributes to tumor development, literature data on its function allow to draw several speculations on how this might occur, as described below.

3. Haspin functions and potential tumor-supportive effects

3.1. Impact of Haspin on mitotic chromosomal dynamics

Cancer cells often exhibit chromosomal aberrations and aneuploidies, with about 90% of human tumors being aneuploid [35], representing the most recurrent genetic alteration of malignant tissues. Although the exact contribution of aneuploidies to cancer development has not been fully comprehended, aneuploidy has been observed to often correlate with pro-oncogenic features [35–37]. It is thought to promote genomic instability, favoring the insurgence of DNA mutations, karyotype evolution and an overall improved fitness of malignant cells [38]. Thus, understanding and tackling the mechanism regulating chromosome segregation and, hence, aneuploidy insurgence, is a paramount goal for an improved management of tumors.

3.1.1. H3-Thr3p as a local landmark to recruit the chromosomal passenger complex

The first functional characterization of Haspin came from Higgins' group in 2005, when Dai et al. reported the presence of histones in a human Haspin immunoprecipitate and the direct phosphorylation of human H3-Thr3 by Haspin [11], a modification reverted at the end of mitosis by the activity of RepoMan-PP1 [39]. In the same work, Dai and colleagues showed that loss of Haspin also causes failures in chromosome alignment on the metaphase plate hence promoting chromosome missegregation events [11]; this study first established a contribution of Haspin activity to a successful mitosis. In the next few years, other works

Table 1
Effects of Haspin loss on tumors. Haspin expression levels (second column, either measured as protein or transcript abundance) and given Haspin-related phenotypes (third to seventh columns) are reported as measured on indicated primary tumors or models (first column). *: upon loss of Haspin activity; n.s.: not statistical correlation detected; grey cells: given phenotype has not been assessed in the corresponding biological sample.

Tumor	Expression levels	Correlation Exp/tumor grade	Correlation Exp/survival	Cellular proliferation*	Xenograft growth*	Migration*	Reference
Skin	Higher			Reduced	Reduced	Reduced	[18,31,33,34]
Lung	Higher			Reduced			[18]
Colon	Higher			Reduced	Reduced		[18,30,32,33]
Bone	Higher						[19]
Pancreas	Higher	Positive	Negative		Reduced	Reduced	[20]
Gallbladder	Higher	Positive		Reduced	Reduced		[21]
Prostate	Higher	Positive		Reduced	Reduced		[20,22,27]
Bladder	Higher	Positive	Negative	Reduced	Reduced		[23]
Ovaries	Higher	Positive	Negative	Reduced			[24,30]
Breast	Higher	n.s.	Negative	Reduced			[25,27,28,30]
Bile duct	Higher	Positive			Reduced	Reduced	[26]

further extended the number of processes impacted by a downregulation of Haspin, and begun to draw a connection between Haspin and the chromosome passenger complex (CPC) [40], a protein complex made up of Aurora B, Survivin, Borealin and INCENP able to drive the response to chromosome misattachments to the mitotic spindle and prevent aneuploidies [11,41]. However, it was not until 2010 that the mechanism linking Haspin-mediated phosphorylation of H3-Thr3 with chromosome segregation was unveiled by three distinct groups led Higgins, Funabiki and Watanabe. Working independently in human, *Xenopus* or yeast models respectively, they came to the same conclusion that Survivin directly binds H3-Thr3p to direct CPC at inner centromeric regions in mitosis [13,42,43] (while a distinct pool of the CPC is recruited to kinetochore-proximal centromeric regions through Bub1-dependent H2A-Thr120p [13,44–46]); a milestone that has been extended in the upcoming years leading to a deep comprehension of the intimate interplay between Haspin, CPC and mitotic chromosome segregation.

Given its delicate role, the activity of Haspin must be tightly regulated so that unscheduled H3-Thr3 is prevented. This occurs thanks to the presence of the aforementioned autoinhibitory domain that prevents the interaction between the catalytic core and its substrate during interphase. The inhibitory domain is displaced as cells approach mitosis, via a cascade of phosphorylation events by mitotic kinases. Haspin mitotic activation is thus a tripartite process consisting of an initial activation in early mitosis by CycB-CDK1, followed by the phosphorylation of Haspin-Thr128 by PLK1 and a concomitant recruitment of the CPC to the chromatin, where Aurora B can further phosphorylate Haspin [9,10,41]. This generates a feedback loop that, also thanks to the contribution of the Bub1/Shugoshin pathway, leads to the buildup of a consistent CPC pool at inner centromeres, where it targets multiple kinetochore subunits that trigger activation of the spindle assembly checkpoint and the consequent cell-cycle arrest in presence of spindle misattachments preventing errors in chromosome segregation and the insurgence of aneuploidies (Fig. 1).

3.1.2. *Haspin prevents unscheduled cohesin cleavage*

Loss of Haspin activity was also shown to lead to a general loss of sister chromatids cohesion, though the underlying mechanism was not initially undisclosed [40].

Following DNA replication, a tight cohesion of sister chromatids is ensured by the cohesin complex, a ring-shaped protein complex whose core subunits are Smc1, Smc3, Scc1 and Scc3/SA [47–51]. Removal of cohesin is a tightly regulated process in the cell-cycle. Before mitosis, cohesin is stably associated to sister chromatids. In prometaphase and metaphase most cohesin complexes are phosphorylated by Wapl and removed from chromosome arms, accounting for the detachment of a sister's pair along their arms [52–56]. Yet, to sustain the amphitelic attachment and alignment of chromosomes on the metaphase plate, the sister chromatids must maintain a robust connection at centromeric regions, which is ensured by the localized persistence of a cohesion pool until anaphase [57,58]. This balance of local cohesin maintenance/removal is guaranteed by a delicate mechanism based on a competition between accessory cohesin stabilizers and dissociation factors.

Among these, the essential cohesin-binding protein PDS5 is particularly relevant to both the function and regulation of the cohesin complex [59]. Indeed, PDS5 promotes the establishment, maintenance and resolution of sister chromatid cohesion by differential recruitment of accessory proteins according to the cell-cycle stage. In S-phase, PDS5 interaction with ESCO1 and ESCO2 leads to cohesin stabilization through Smc3 acetylation [60–65]. Then, loss of sister cohesion through G2 is prevented by binding of Sororin to Pds5, which competes with and impedes binding of the cohesin dissociation factor Wapl [51]. Later in the cell cycle, Sororin is displaced following phosphorylation by mitotic kinases [66,67], allowing binding of Wapl to Pds5 and cohesin removal from chromosome arms. Centromeric regions maintain cohesion thanks to the recruitment of Shugoshin [68], which competes with Wapl for binding with Pds5 [69–71], protecting centromeric cohesion from phosphorylation.

Haspin recruitment to centromeric regions was shown to rely on

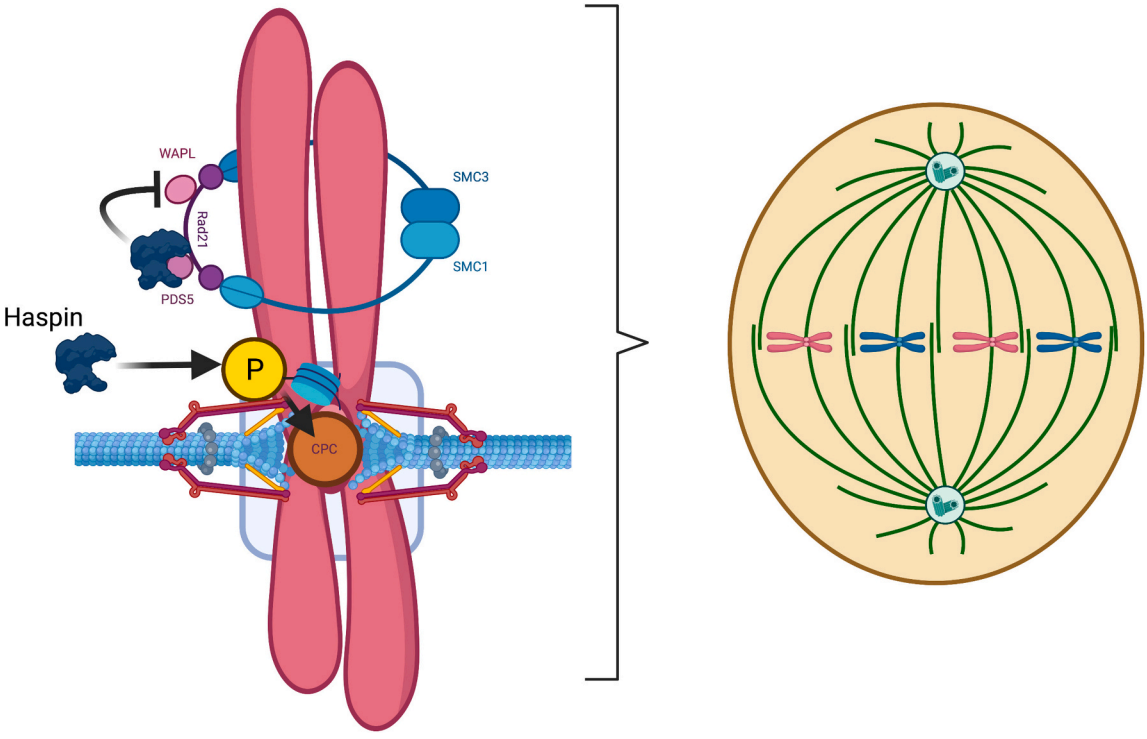

Fig. 1. Haspin is required for proper maintenance of chromosome stability – Haspin plays a pivotal role throughout mitosis through inhibition of Wapl (both by direct physical interaction with Pds5 and through phosphorylation of Wapl itself) and recruitment of the CPC through phosphorylation of H3-Thr3. These two effects, combined, ensure proper chromosomal dynamics and a correct mitosis.

Pds5 in *S.pombe* [13] and this, along with its impact on sister chromatid cohesion [40], strongly suggested a functional impact of Haspin in the regulation of the Wapl/Sororin competition for Pds5 binding. Moreover, the initial accumulation of both Haspin and H3-Thr3 on chromosome arms in early mitosis, followed by relocalization towards centromeric regions in metaphase [11] was consistent with the timing of cohesin removal, further corroborating the hypothesis of an involvement of Haspin in such process.

Indeed, it was later found that Haspin Pds5-interacting domain and Pds5 Haspin-interacting domain are both required for localization of Haspin to centromeric regions in a Topoisomerase II dependent manner [72] and that Pds5 domains involved in Haspin recruitment are the same that mediate centrosomal localization of Wapl [72,73], clearly demonstrating a competition of the two proteins for recruitment at these regions.

In agreement with this, loss of Haspin results in a weaker cohesion at centromeres during mitosis [73]. Remarkably, in human Haspin-KO cells, expression of the N-terminal Haspin domain (Haspin1–50) is enough to support a functional shielding of cohesin from Wapl-mediated displacement [73], demonstrating a structural, kinase-independent role for Haspin in this process. On top of this, Liang et al. later found that Haspin directly interacts with and phosphorylates the N-terminus of Wapl preventing Wapl interaction with Pds5 [74]. Such findings show a direct role for Haspin in the prevention of unscheduled cohesin removal through inhibition of Wapl (Fig. 1).

Thus, Haspin orchestrates the delicate process of chromosome segregation by both overseeing CPC functionality and cohesin stability, overall promoting euploidy maintenance and preventing detrimental loss/gain of genetic material. Given its roles in mitosis, the need for Haspin for the cell survival is expected to scale with the proliferation rate of the cell itself, rendering it particularly relevant to cancer cells. Accordingly, as mentioned above, Haspin levels highly correlate to the proliferative rate of breast cancer cells and loss of CPC subunits has been reported to reduce tumor growth [75–79].

3.2. Haspin promotes primary cilia-resorption

Remarkably, regulation of chromosome segregation is not the only role exerted by Haspin, but rather, multiple other pathways regulated by Haspin activity with a putative tumorigenic potential are rapidly emerging.

Apart from the aforementioned “direct” roles of H3-Thr3 phosphorylation, this histone modification comes with a “side-effect” consisting in the displacement of a multitude of proteins from the adjacent H3-Lys4me$_3$ [80,81], so that a loss or an increase of Haspin activity might lead to complex, at first unexpected, phenotypes. An example relevant for this review is the displacement from the chromatin of the isoform 3 of the Death Induced Obliterator (DIDO3) and the role this protein plays on cilia dynamics [82].

Primary cilia are tubulin-based organelles present in virtually all non-cycling cells, with a plethora of roles [83–87], which are nucleated from a matured version of the centrosome, known as the basal body, incapable to sustain a mitotic apparatus [88]. Thus, given that the number of centrosomes in the cell is tightly regulated to never exceed 1 outside of mitosis, the maturation of the centrosome into a basal body acts as a wall against unscheduled cell proliferations and cancers [89,90], and accordingly most human tumors do not show any primary cilium on the surface of their cells [91,92], while normal resting cells present cilia on their surface. When needed, however, the tubulin in the cilium is deacetylated following activation of the histone deacetylase HDAC6 [93,94], the cilium is resorbed and the basal body is reverted to a centrosome to fulfill its essential mitotic function.

The localization of HDAC6 relies on direct binding to DIDO3 [82], which normally decorates H3Lys4me$_3$ residues in non-mitotic cells. We have recently showed, both in human cell cultures and *D.rerio* embryos, that the length of the primary cilium and its resorption are both controlled by Haspin [17]. In fact, we showed that Haspin phosphorylates H3-Thr3 even in quiescent cells, and that this in turn promotes cilia resorption likely acting on the DIDO3-HDAC6 axis, as a DIDO3 mutant that does not bind H3-Lys4me3 bypasses the requirement for Haspin activity [17]. This pathway is likely relevant in the context of carcinogenesis, as elevated expression of Haspin would lead to increased H3-Thr3p levels, thus promoting the recruitment of DIDO3-HDAC6 to the basal body and driving the final cilia resorption and priming the cell for cell-cycle commitment (Fig. 2).

Besides this potent effect, loss of Haspin activity might lead to more subtle defects in cilia functionality still strongly relevant to malignant processes, as several pivotal signaling pathways in tumorigenesis (e.g. Hedgehog, WNT, Hippo) act in a cilia-dependent manner [91], but further works will be required to assess this point.

3.3. Haspin is required for remodulation of cellular polarity

Further extending the comprehension of Haspin and its functions, we recently unveiled a novel role for this kinase in regulating cellular polarization [95–98], defined as the non-random, uneven positioning of landmarks, molecules and organelles within the cell. Cellular polarization is common to virtually all living cells, as they need specialized compartments to fulfill the different metabolic processes essential to their growth. Besides its essential function to cell growth and functions, cellular polarization also acts as a barrier against tumorigenesis [99], and indeed loss of basal-apical polarity is a frequent event at preinvasive stages of carcinogenesis, as it favors the epithelial to mesenchymal transition [100–103]. Thus, mechanisms aiming at the dispersal of polarity clusters might be relevant for tumorigenesis.

We established a first connection between cellular polarity and yeast Haspin paralogues, Alk1 and Alk2 [104] in 2013, when we showed that Haspin mutants exhibited a defective nuclear segregation, with both nuclei being inherited by the daughter cell upon mitotic delays, due to aberrant accumulation of actin and polarity factors [95]. We have later elucidated the underlying mechanism by showing tthat *Sc*Haspin promotes a reprogramming of secretory routes from a polarized to a distributed delivery of vesicles containing GTP-loaded Ras [96,97]. In turn, this triggers a cascade of events that ultimately leads to a redistribution of Cdc42 activity to the whole plasma membrane through relocalization of its GEF Cdc24 [105–107], driving the dispersion of the pre-existent polarity cap [95–97] (Fig. 3). The small GTPase Cdc42 is conserved to all eukaryotes with the essential role to promote and modulate cellular polarization during the cell cycle [108–112]. This protein is particularly relevant to the maintenance of the apical-basal polarity [113,114], so that its loss results in tissue hyperplasia [115]. Moreover, *Sc*Haspin is relevant for the maintenance of a mitotic checkpoint upon failures in polarization, further corroborating a tight link between this kinase and cellular polarity [98]. Remarkably, even though the molecular mechanisms are still missing, these phenotypes are not ascribable to loss of H3-Thr3p [98], suggesting the existence of other, hypothetically non-nuclear, targets of this kinase with the potential to uncouple nuclear and cytoplasmic Haspin functions.

Overall, considering the conservation of all the proteins involved, our observations from budding yeast suggest that an overexpression of Haspin (as observed in tumors) might promote an unscheduled remodulation of physiological polarity clusters, thus favoring the EMT.

4. Concluding remarks

A major goal in treating cancer is to selectively kill transformed cells while sparing normal ones; a way to achieve this is by interfering with processes only active in cycling cells, in an organism mainly made up of non-proliferating ones [116]. The data reviewed in this work thus depict Haspin as an amenable target for antitumoral therapy, as this kinase is at the center of multiple pathways that are particularly relevant for cycling tissues and that collectively exhibit pro-tumoral potential (Fig. 4). First,

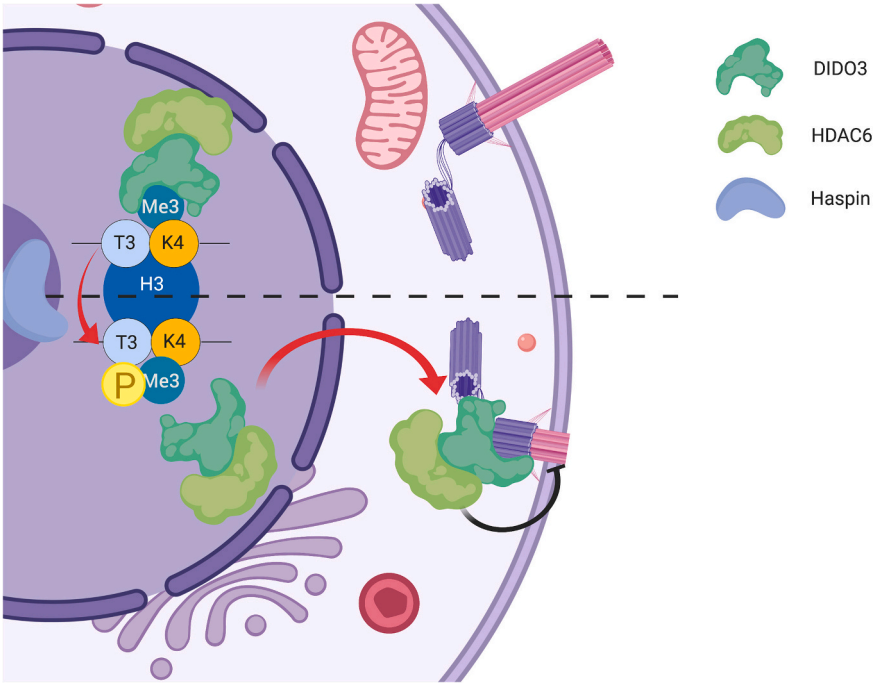

Fig. 2. Haspin favors cilia resorption through H3-Thr3 phosphorylation in quiescent cells. H3-Lys4me3 acts as a hub for DIDO3/HDAC6 recruitment, accounting for physiological dynamics and functionality of primary cilia. Haspin activity counteracts this by phosphorylating H3-Thr3, which, by displacing DIDO3 from the chromatin, causes its accumulation at the basal body, along with a downregulation of the cilium.

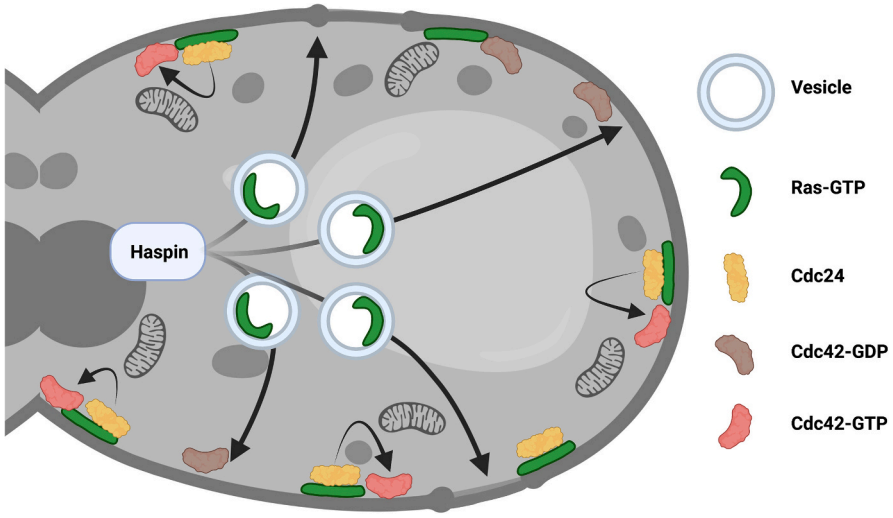

Fig. 3. Haspin promotes an isotropic vesicle delivery to evenly distribute Cdc42 activity at the PM – Haspin is required for an even delivery of Ras-GTP containing vesicle to the PM of daughter cells in budding yeast. Once there, GTP-loaded Ras acts as a hub for the recruitment of Cdc24, which in turn leads to a local activation of Cdc42. This ultimately leads to an isotropic polarization of the cell.

Haspin mediated downregulation of ciliogenesis [17] replenishes the cells of centrosomes ready to sustain the mitotic apparatus, favoring cell cycle commitment and progression. Second, the loss of cellular polarity induced by Haspin [95,96] would promote the EMT and contribute to cellular migration, favoring malignant cell proliferation and spread to the whole organism. Third, the sustainment of chromosome segregation both through CPC recruitment [13,42,43] and cohesin stabilization [72,73] ensures the maintenance of the genetic material, particularly jeopardized by the frequent and rapid mitotic events typical of cancer cells.

Some considerations, though, are needed on the impact of Haspin on genome instability, that is per se a tumorigenic process [117]. Given its role in preventing aneuploidies, Haspin is an important barrier to tumor development, accordingly, several tumors show a loss of heterozygosity in GSG2 [8,29]. Decreased Haspin levels favor genome instability along with a propensity for malignant transformation. At later stages, however, tumors need Haspin activity to prevent excessive genetic material aberrancies, which would be incompatible with cellular survival, to promote mitotic events and to modulate cell polarity, thus promoting tumor expansion. At this stage, unknown molecular mechanisms ensure increased Haspin expression levels even in cells with a single copy of the GSG2 gene [25]. Such a dual mechanism is not uncommon in tumors as highlighted, for example, by components of the DNA damage response, whose loss initially favors tumorigenesis, but that are later needed for

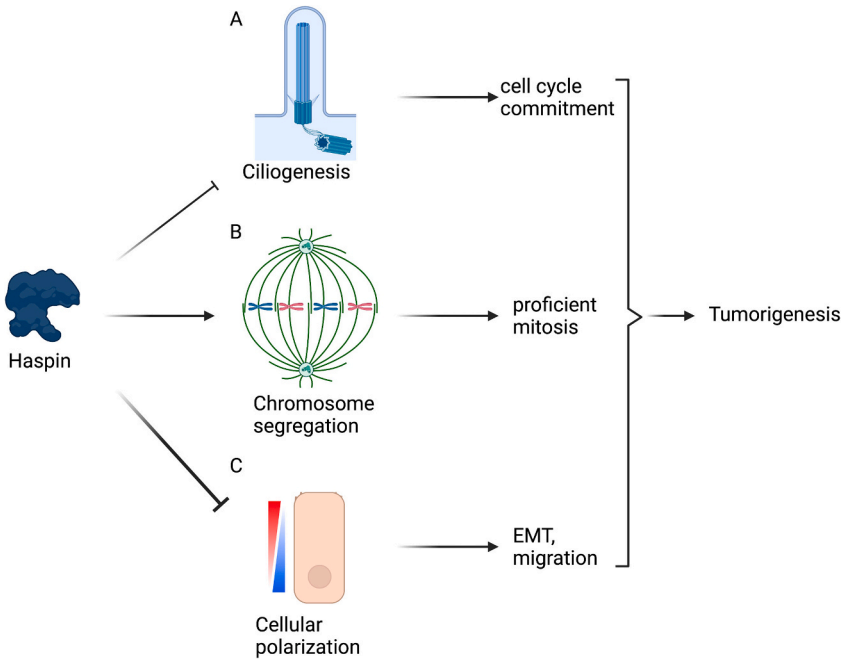

Fig. 4. Haspin-regulated pathways and relative oncogenic potential. Haspin kinase regulates several cellular pathways that might ultimately explain its relevance to tumor growth. (A) Haspin-dependent downregulation of the primary cilium favors cell-cycle commitment. (B) Haspin grants functionality of the CPC and shields cohesin complexes from unscheduled removal, contributing to a functional chromosome segregation. (C) Haspin contributes to the resolution of polarity clusters and loss of polarization, which contributes to the EMT and priming for cellular migration, thus representing a hallmark of cancer cells. Combined, all these factors have the potential to stimulate and support cellular proliferation, and thus, carcinogenesis.

cancer cell survival and accordingly exploited as therapeutic targets in several chemotherapeutic approaches [118].

To conclude, although a lot of effort is still needed to understand the exact mechanisms underlying Haspin contribution to tumors, the mentioned impact of its loss on malignant cells, its peculiar kinase domain that supports selectivity of chemical inhibitors, and the considerations on its suitability as a therapy target are strong prerequisite making Haspin amenable for further studies with the final aim to exploit it as a target to specifically kill tumor cells. A potential *caveat* to this comes from over a decade of unsuccessful clinical trials on mitotic kinase inhibitors, that were ultimately rejected due to the fact that such treatments "selectively" kill cells based on their proliferative rate, but the human body hosts normal tissues (eg: bone marrow) that proliferate several times faster than any tumor and that would be killed as well generating a high toxicity (reviewed in: [119]). That being said, the notions that CHR-6494 did not cause any toxicity in murine models [30] and viable Haspin KO mutants have been obtained several organisms [16,95,120] make Haspin an ideal candidate for translational approaches leading to clinical trials.

Acknowledgments

Research in M.M-F lab is supported by AIRC (15631 and 21806), Telethon (GGP15227), MIUR. RQ was supported by an AIRC fellowship (17919). We thank Federico Lazzaro and all the members of the laboratory for critical discussions. Figures were created with BioRender.com:

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