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Review

Crosstalk between kinases, phosphatases and miRNAs in cancer

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ABSTRACT

Reversible phosphorylation of proteins, performed by kinases and phosphatases, is the major post translational protein modification in eukaryotic cells. This intracellular event represents a critical regulatory mechanism of several signaling pathways and can be related to a vast array of diseases, including cancer. Cancer research has produced increasing evidence that kinase and phosphatase activity can be compromised by mutations and also by miRNA silencing, performed by small non-coding and endogenously produced RNA molecules that lead to translational repression. miRNAs are believed to target about one-third of human mRNAs while a single miRNA may target about 200 transcripts simultaneously. Regulation of the phosphorylation balance by miRNAs has been a topic of intense research over the last years, spanning topics going as far as cancer aggressiveness and chemotherapy resistance. By addressing recent studies that have shown miRNA expression patterns as phenotypic signatures of cancers and how miRNA influence cellular processes such as apoptosis, cell cycle control, angiogenesis, inflammation and DNA repair, we discuss how kinases, phosphatases and miRNAs cooperatively act in cancer biology.

1. Introduction

Phosphorylation and dephosphorylation are the main type of post-translational modifications in eukaryotic cells, and are tightly regulated by protein kinases and protein phosphatases, respectively [1]. Indeed, phosphorylation and dephosphorylation are efficient strategies to modulate cellular response towards internal and external stimuli, since it is a reversible process that does not require synthesis and/or degradation of proteins. Therefore, these post-translational modifications allow cells to transiently regulate a set of proteins at the same time, in different cellular compartments and signaling pathways that in turn, define which metabolic response will be dominant under a specific stimulus. Under this context, a variety of cellular processes, such as proliferation, migration, apoptosis, autophagy, differentiation, metabolism, organelle trafficking, immunity, learning and memory depend on the action of kinases and phosphatases [2–4]. Thus, not surprisingly, abnormal kinase or phosphatase activities correlate with disease conditions such as cancer, diabetes and neurodegenerative or inflammatory disorders [5–7].

Specifically in relation to miRNAs metabolism and function, there are some evidences that kinases and phosphatases can be modulated and modulate miRNAs. Recent studies have proposed that oncogenic miRNAs can downregulate the expression of tumor suppressor kinases and phosphatases, which in turn contributes for tumor progression. The interplay between protein kinases, phosphatases and miRNAs in cancer cells is very complex and depends of many features, such as cell type and tumor context, as well as the pattern of expression of tumor suppressor and oncogenic miRNAs. Therefore, it is clear that the complex crosstalk between protein kinases, phosphatases and miRNAs can contribute to increase cancer aggressiveness, giving tumor cells the ability to survive, increase proliferation, evade cell death routines and metastasize. This review will highlight what is already known about the interplay between miRNAs, protein kinases and phosphatases and its importance in cancer. Besides, we also highlight the potential of those molecules as targets for more efficient cancer therapy.

1.1. Post translational modification: role of protein kinases and phosphatases

About 2% of the human genome correspond to protein kinases, encoding 518 protein kinases, which constitute one of the largest gene families in eukaryotes [3,8,9]. Protein kinases (PKs) catalyze the phosphorylation on serine, threonine or tyrosine residues.

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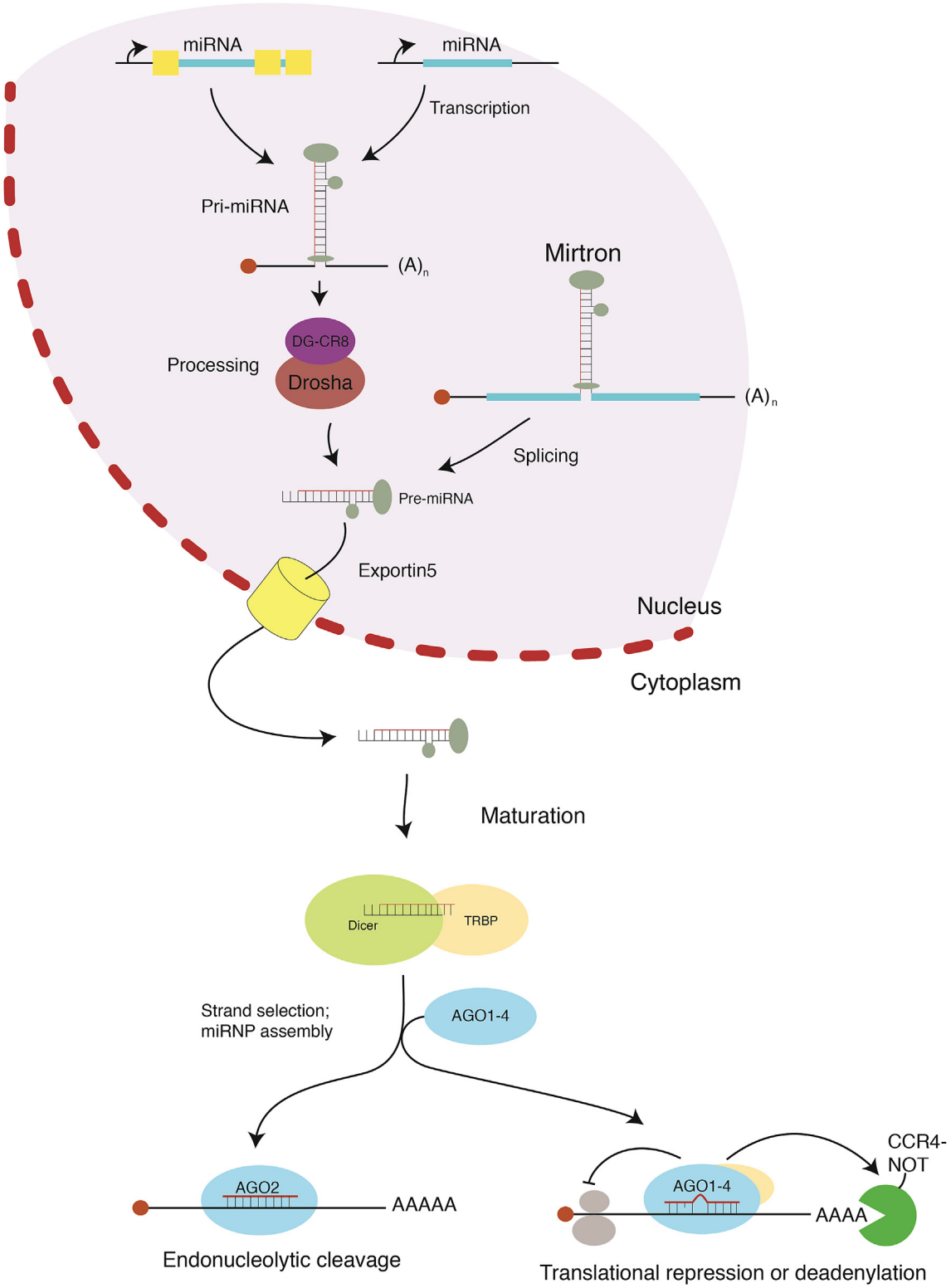

Fig. 1. Biogenesis of miRNA. Pre-miRNAs generated by the canonical or non-canonical pathways are transported by an exportin 5 and RAN-GTP-dependent process from the nucleus to the cytosol. The precursors are further processing by the Dicer and transactivation-response RNA-binding protein (TRBP) RNase III enzyme complex to form the mature double-stranded miRNA. Next, argonaute proteins facilitate incorporation of the mature miRNA-targeting strand into the AGO-containing RNA-induced silencing complex (RISC). The RISC-miRNA assembly is then guided to specific target sequences in mRNAs resulting either in translational repression or decreased mRNA stability.

Thus, based on the nature of the phosphorylated group, kinases are classified as protein-serine/threonine kinases (385 members), protein-tyrosine kinases (90 members), and tyrosine-kinase like proteins (43 members) [3,10].

By contrast, the human genome encodes only approximately 200 phosphatases, targeting phosphorylated proteins or lipids. Protein phosphatases (PPs) catalyze the hydrolysis of the phosphate group from its protein substrate. Thus, PPs are categorized by

structure and substrate specificity into protein serine/threonine phosphatases (PSTPs, approximately 30 members) and protein tyrosine phosphatases (PTPs, 107 members) [10,11].

1.2. Biogenesis and function of miRNAs

MiRNAs (miRNAs) are small non-coding RNA molecules that contain around 19–30 nucleotides (on average 20 nucleotides) and are produced by the canonical or non-canonical biogenesis pathways [12]. miRNAs generated by the canonical biogenesis pathway are synthesized as precursor RNAs from intergenic, intronic or polycistronic genomic loci by RNA polymerase II. Subsequently, Drosha and DGCR8 RNase III complex recognize and process the stem-loop structure of primary miRNA (pri-miRNA) transcript. In contrast, non-canonical miRNA biogenesis directly produces miRNAs as endogenous short hairpin RNAs or derives directly through splicing from introns that can refold into hairpins (mirtrons). Exportin 5 transports both precursors (pre-miRNA and mirtrons) (~60–100 nucleotides) from the nucleus to the cytosol in a Ran–GTP dependent manner. Subsequently, the precursors are processed by a complex consisting of Dicer and transactivation-response RNA-binding protein (TRBP) RNase III enzymes, to form the mature double-stranded miRNA. Next, argonaute proteins facilitate incorporation of the mature miRNA-targeting strand into the AGO-containing RNA-induced silencing complex (RISC). The RISC-miRNA assembly is then guided to specific target sequences in mRNAs. The initial recognition of mRNAs by the RISC-miRNA complex is driven primarily by base-pairing of nucleotides 2 to 8 in the mature miRNA with specific mRNA target sequences located in the 3′ untranslated region (3′UTR), and additional base-pairing affords greater affinity and targeting efficiency. The RISC-miRNA complex acts either in translational repression or decreasing mRNA stability [12] – (Fig. 1). However, in some cases miRNAs can enhance mRNA translation. For instance, it was reported that miR-10a binds to 5′UTR of ribosomal protein mRNAs and enhanced their translation [13].

In general miRNAs are believed to target about one-third of human mRNAs and a single miRNA is capable of targeting approximately 200 transcripts simultaneously [14–16]. Therefore, miRNAs have been implicated in almost every biological process, including development, cell cycle regulation, cell growth and differentiation, stress response, and apoptosis. In addition, miRNAs play a role in a variety of diseases, particularly in cancer [17].

1.3. miRNAs and cancer

In addition to maintaining the normal growth, development, and health of an organism, miRNAs can also influence the development and progression of malignancy. Since around 50% of human miRNAs are located in fragile chromosomal regions, which may exhibit DNA amplifications, deletions or translocations during tumor development, their expression is frequently deregulated in cancer [18,19]. Besides, it has been observed that cellular transformation and tumorigenesis can be promoted by suppression of key components of miRNA processing machinery. Widespread dowregulation of miRNAs is often detected in human cancers such as breast, ovarian and prostate cancer. In general, miRNAs can function either as tumor suppressors or as oncogenes (oncomirs), initiating tumor growth, invasion, metastases, as well as regulating the overall *stemness* of cancer cells [20].

1.4. miRNA as endocrine signals

Very recent papers in the literature have reported that miRNAs can be detected in the human plasma, suggesting possibilities for novel disease biomarkers and the intriguing notion that some miRNAs may serve regulatory purposes in target cells. In the plasma, miRNAs can be found as part of microvesicles and exosomes derived from donor plasma membranes cells, in association with the miRNA-processing enzyme argonaute 2 and in lipoproteins [21]. It has been proposed that vesicles (microvesicle/exosomes) containing miRNAs are delivered to target cells either by a process involving endocytosis or by membrane fusion [21]. Importantly, it also has been shown that circulating miRNAs might rather act as endocrine or paracrine signaling molecules to deliver a regulatory signal from donor to target cells. These mobile miRNAs, defined as *hormomirs* due to their hormone-like characteristics, could act as local or long-range signals to maintain normal homeostasis or influence the development and progression of diseases such as cancer. Different research groups have isolated cell-free circulating miRNAs from blood and demonstrated that the levels of certain miRNAs changed in response to various tumors, which pointed out these molecules as non-invasive biomarkers for different tumor entities [22]. However, the functional significance of circulating miRNAs is still not clear, and this might be, at least in part, due to non-reproducibility of data, as Jarry and collaborators have addressed in a review [23].

2. Influence of protein kinases and protein phosphatases in miRNAs biogenesis

2.1. Regulation of Drosha and Dicer stability and processing activity

Following the discovery of miRNAs and their potential significance to orchestrate the whole cellular machinery, a renewed understanding shed lights to a more comprehensive and straightforward view towards the dynamic balance of miRNAs generation. The primordial and limiting step in miRNAs biogenesis relies on the Drosha/DGCR8 holoenzyme. The translocation of Drosha to the nucleus is known to be activated by GSK3β, through a specific phosphorylation at the N-terminal nuclear localization domain [24]. In the nucleus Drosha selects precursor transcripts to efficiently produce a global stream of functionally relevant miRNAs *in vivo*. Therefore, the selectivity of Drosha gives insights into why, of the hundreds of thousands of potential miRNAs, only a subset is ever produced by cells [25].

As mentioned before, following translocation into the cytoplasm, the pre-miRNA is cleaved near the terminal loop by the RNase III domain of Dicer to generate a 22-nucleotide double strand mature miRNA. Several Dicer-associated proteins have been identified, including TAR RNA-binding protein (TRBP) and protein kinase R-activating protein (PACT). Dicer stability and activity are enhanced by association with TRBP and PACT [26] and depletion of these cofactors decreases the steady state levels of Dicer protein [27,28]. Furthermore, cell-signaling pathways can also modulate the expression or activity of Dicer. For instance, MAPK/ERK signaling was shown to promote the phosphorylation of TRBP [29]. Phosphorylated TRBP increases miRNA production by increasing the stability of Dicer. Besides, the activating oncogenic mutation $Braf^{V600E}$ (upstream mediator of MAPK cascade) amplifies the processing of pri-miRNAs into mature miRNAs, overcoming even the loss of Dicer expression induced by haploinsufficiency in primary mice sarcomas. Comparison with the opposite mutation in *Kras* genes reinforced that deficient MAPK activity leads to decreased steady-state levels of mature miRNAs, which has been associated with tumor progression and development of metastases [30].

Protein tyrosine phosphatase also seems to take part in miRNA biogenesis. For instance, chemoresistant chronic myeloid leukemia cells with reduced expression levels of low molecular weight protein tyrosine phosphatase (LMW-PTP) exhibit lower expression of

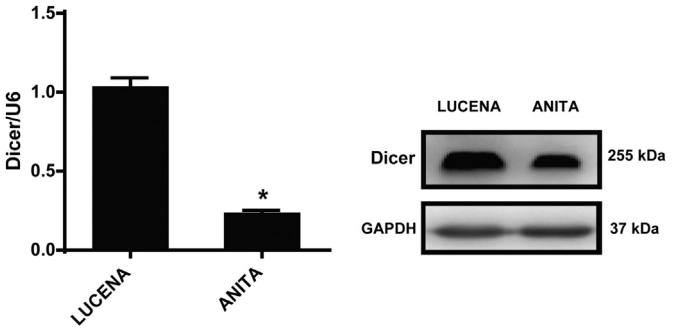

Fig. 2. Protein expression analysis of Dicer expression levels in two chronic myeloid leukemia cell lines. Lucena, derived from K562, is chemoresistant through overexpression of P-glycoprotein. Anita, derived from Lucena is a stable knockdown of LMW-PTP accomplished using shRNA in stable transfection with lentiviral particles.

Dicer. This can be observed at both mRNA and protein levels (Fig. 2). We have previously reported that LMW-PTP contributes for CML resistance [31]. However, it is still not clear if there is a connection between this phosphatase, miRNA synthesis and CML resistance.

2.2. miRNA decay regulation

Despite some miRNA biogenesis regulatory mechanisms having been described, the control of mature miRNAs life span through degradation has received less attention. miRNAs appear as highly stable molecules, since mature miRNAs have been found to persist for many hours or even days after their production [32–34]. Besides, mature miRNAs have been also found to be expressed in a tissue- or stage-specific manner without variation in the expression pattern of the precursor forms (pri- and pre-miRNAs), suggesting a regulatory mechanism acting on the mature miRNAs [35]. Some metabolic conditions such as cell cycle, viral infection, exposure to growth factor and endoplasmic reticulum stress have been shown to affect miRNA stability [36–38]. However, whether kinases and/or phosphatases are able to participate and mediate miRNAs degradation remain to be investigated in details, but those proteins may have crucial roles in this process. For instance, it has been shown that the exposure of breast and brain tumors to growth factor, such as epidermal growth factor (EGF), causes a fast variation on specific miRNAs and transcription factor levels. Indeed, EGFR, a tyrosine kinase receptor, activation in those cells provoked a decrease of the amount of 23 miRNAs, and consequently, rapid induction of oncogenic transcription factors [38]. Another enzyme that has been shown to play an important role in controlling miRNAs life span is the endoplasmic reticulum transmembrane kinase-endoribonuclease (IRE1α). IRE1α is a multifunctional protein that consists of three important regions, an N-terminal sensor domain located inside of endoplasmic reticulum (ER) that detects misfolded proteins, a transmembrane region, and a cytosolic tail containing two distinct catalytic activities: a serine/threonine kinase and an endoribonuclease (RNase). Under ER stress, when there is an increase of misfolded proteins, an oligomerization with subsequent autophosphorylation of IRE1α can be observed. This, in turn, allosterically activates its RNase activity [39,40]. Upton et al. [41] have reported that sustained IRE1α RNase activation caused rapid decay of select miRNAs (miRs -17, -34a, -96, and -125b) that normally repress translation of Caspase-2 mRNA. This, consequently, elevates Caspase-2 concentration and favors the mitochondrial apoptotic pathway. Besides, in cell-free systems, recombinant IRE1α endonucleolytically cleaved miRNA precursors at sites distinct from Dicer, which indicates that IRE1α regulates translation of a proapoptotic protein through terminating miRNA biogenesis [41].

2.3. Phosphatidylinositide 3-kinase (PI3K) modulates the level of exportin

PI3K is involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival and intracellular trafficking. Therefore, when dysfunctional, PI3K displays a pivotal role in cancer progression. This enzyme produces the main positive modulator of AKT, PtdIns(3,4,5)P3. Recently, Iwasaki et al. [42] have compared the miRNA expression profiles between resting and antigen-activated lymphocytes and also in primary mouse embryonic fibroblast (MEF). In activated T-cell population an elevation of a broad numbers of miRNA was observed, and this profile was similar in MEF cells. Interestingly, in the same study the authors showed that exportin 5 was induced during cell cycle entry by a PI3K-dependent post-transcriptional mechanism. In addition, the inhibition of exportin 5 expression interfered with global miRNA elevation and resulted in a proliferation defect associated with delayed G1/S transition. Iwasaki et al. [42] also suggested that exportin 5-mediated global miRNA elevation might be involved in a broad range of cellular events associated with cell cycle control.

2.4. Phosphatase of regenerating liver-3 (PRL-3) upregulates the expression of miRNAs

PRL-3 a member of the classic protein tyrosine phosphatase family has received significant attention because of its involvement in colorectal cancer (CRC) metastasis. High expression of PRL-3 was observed especially in metastatic lesions derived from primary CRC, regardless of the target organ [43]; however, its expression was low or absent from normal colorectal epithelia, adenomas and primary lesions [44]. Zhang et al. [45] reported that PRL-3 upregulates the expression of miR-21, miR-17 and miR-19a in both colon cancer cells and tissues by activating signal transducer and activator of transcription 3 (STAT3) via the Csk-Src-STAT3 pathway. These data suggest a connection between PRL-3 and tumor metastasis.

3. Modulation of protein kinases by miRNAs

Several oncogenic and tumor suppressor kinases have been shown to be targeted by miRNAs in human cancers (Table 1). The altered expression of these proteins can result in some typical features of tumor cells, including resistance to apoptosis and an improved ability of migration and invasion. Some of these kinases and phosphatases, as well as the miRNAs described as their regulators, will be presented and their role in tumor progression will also be discussed. A summary of the main downstream signaling pathways altered by these proteins and the subsequent cellular responses is presented in Figs. 3 and 4.

3.1. Cell cycle kinases

In this section we addressed kinases that regulate the cell cycle progression and miRNAs that target them. The majority of those miRNAs function as tumor suppressors and they are inactivated in cancer by different mechanisms (reviewed by Bueno and Malumbres, 2011 [46]). For instance, miR-124 and miR-137 are silenced by hypermethylation in different human tumor cells which lead to CDK6 overexpression [47].

3.1.1. Cyclin-dependent kinases (CDKs)

CDKs are serine/threonine kinases that play a key role in cell cycle regulation. Specific CDKs are activated in different phases of

Table 1
Regulation of protein kinases by miRNAs in cancer.

Kinase	Examples of substrates	Regulatory miRNAs	Protein data	Altered miRNA expression
CDK4	Cdt1, Marcks, p107, p130, retinoblastoma, SMAD3	miR-34 [53], miR-195 [54] and miR-506 [199]	Overactive in human cancers due to genetic and epigenetic alterations [52]	Ectopic expression of miR-506 in ovarian cancer cells inhibits proliferation [199]
CDK6	Bcl2, Histone H1, retinoblastoma	miR-22 [55], miR-29 [56], miR-34 [57], miR-107 [58,59], miR-124a [60], miR-125b [61], miR-129 [62], miR-137 [63], miR-186 [64], miR-191 [65], miR-195 [66], miR-218 [67], miR-449a [68] and miR-494 [69]	Overactive in human cancers [52]	Expressive tumor growth inhibition and survival improvement were observed in mice bearing TP53-mutated multiple myeloma xenografts treated with miR-34a mimics [200]
CDK2	CDK7, E2F, p27, retinoblastoma, p53	miR-186 [64], miR-372 [70] and miR-885-5p [71]	Overactive in human cancers [52]	Ectopic expression of miR-372 suppressed cell growth and induced arrest in the S/G_2 phases of cell cycle in HeLa cells [70]
CDK1	Casein kinase 2, CDK7, APC	miR-16 (Takeshita et al., 2010), miR-223 [72], miR-410 [73], miR-650[73], miR-1699, miR-1744 and miR-1798 [72]	Overactive in human cancers [52]	miR-16 significantly diminished the growth of prostate tumors in bone metastasis model [201]
Aurora	Histone H3, Aurora B, INCENP (CPC subunit), Ndc80, KNL1, Dsn1 and vimentin [202]	miR-24 [76] and let-7a [77]	Aberrant expression of Aurora kinases can disturb checkpoint functions leading to genetic instability and cancer onset. Overexpression of Aurora kinases has been detected in several cancer types and correlates to a poor prognosis [75]	Downregulation of let-7 has been detected as a common feature in several cancers, such as breast, colon, and lung cancers [78–80]; overexpression of let-7a inhibited the growth of HeLa cells by targeting Aurora kinase B [77]
Cdc7	MCM2-7 complex, ORC 1L [85]	miR-29a [88]	Cdc7 is overexpressed in human cancer cell lines and many primary tumors [86]. When overexpressed Cdc7 enhances tumor cell survival by repairing stalled replication forks [87]	Ectopic expression of miR-29a in lung cancer cells prevented Cdc7 accumulation in response to BPDE resulting in altered checkpoint signaling and increased cell death [88]
PLK1	Cdc25C, anaphase-promoting complex (APC), abnormal spindle (Asp) a microtubule-associated protein [93]	miR-10b [104], miR-100 [105,106] and miR-593 [107]	Overexpressed in cancers, including breast cancer [90], ovarian cancer [91], endometrial carcinomas [92], pancreatic cancer [93], renal carcinoma [94], colorectal cancer [95] and melanoma [96]	Ectopic expression of miR-10b decreased PLK1 expression and inhibited breast cell proliferation *in vitro* and tumor growth *in vivo* [104]. In naso-pharyngeal cancer cells transfected with miR-100 mimics exhibited reduced PLK1 expression and underwent growth inhibition, G2/M cell cycle arrest and apoptosis [106]. Synthetic miR-593 suppressed PLK1 expression in EC cells and reduced cell proliferation and increased the number of cells in the G2/M phase [107]
Wee1	cyclin B-CDK1 complex [108]; histone H2B [109]	miR-128a miR-155, miR-516a-3p [110] and miR-497 [111]	Highly active in several types of cancer, especially those ones that display p53 deficiency [203]	miR-128a, miR-155 and miR-516a-3p were shown to be overexpressed in nonfunctional pituitary adenomas [110]. Ectopic expression of these miRNAs in HeLa cells inhibited Wee1 expression, which was intriguingly accompanied by a decrease in cell proliferation [110]. siRNA knockdown of Wee1 in neuroblastoma cells increased apoptosis, while the overexpression of miR-497 reduced cell viability, increased apoptosis and sensitize neuroblastoma cells to treatment with cisplatin [111]
ATM	Chk1, Chk2 [52,56], histone H2A, p53 and Mdm2			Overexpression of miR-101 was shown to sensitize tumor cells to

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Table 1 (*continued*)

Kinase	Examples of substrates	Regulatory miRNAs	Protein data	Altered miRNA expression
		miR-101 [115], miR-100 [114], miR-421 [116]	ATM gene alteration is a frequent event in pathogenesis of chronic lymphocytic leukemia [204]	radiation *in vitro* and *in vivo* by targeting ATM kinase [115]. Hu and colleagues [116] showed that HeLa cells overexpressing miR-421 were not able to block DNA synthesis in the S-phase of the cell cycle (S-phase checkpoint) in response to DNA damage. This effect was mediated by ATM downregulation and contributed to increase radiosensitivity in HeLa cells [116]
ATR	Chk1, Chk2 [52,56], HDAC2, p53 [205,206]	miR-185	Upregulated in Oral squamous cell carcinoma [207]	miR-185 was shown to be downregulated by ionizing radiation in renal cell carcinoma tissues and cell line [117]. Overexpression of miR-185 sensitized renal carcinoma cells to radiation both *in vitro* and *in vivo* [117]
MST2	YAP (Yes-associated protein) and TAZ (co-activator with PDZ-binding motif) [123,124]	miR-133b [120]	Overexpressed in human cervical carcinomas [120]	
LATS2	Aurora A	miR-31 [127], miR-372 [128,129] and miR-373 [128,130]	Tumor suppressor through modulating different processes such as cell proliferation and cell death ([121–123]	miR-31 was found to be overexpressed in murine and human lung cancers cells, and the knockdown of miR-31 increased LATS2 expression and repressed growth and tumorigenicity of these cells [127]. In human gastric cancer cells the inhibition of miR-372 by using antisense miR-372 oligonucleotide increased LATS2 expression, induced cell cycle arrest, suppressed proliferation and increased apoptosis of these cells [129]
BcrAbl	Src, Stat5 [208], uracil DNA glycosylase UNG2 [208,209]	miR-203 [131], miR-29b [132] and miR-30a [133]	hallmark in chronic myelogenous leukemia	miR-203 is silenced in CML; ectopic expression of miR-203 reduces ABL1 and BCR-ABL1 expression and inhibits cell proliferation [131]. Overexpression of miR-30a in K562 leukemia cells reduced ABL1 and BCR-ABL1 protein expression, proliferation, and blocked cell cycle progression between G1 and S [133]
PKC	AKT1, ATF2, BAD, CX43, IRS1, MET, PKC epsilon and STAT3 [203]	miR-31 [135]	Highly activated in cancers [210]	Enhanced expression of miR-31 provokes an inhibition of the oncogenic NFκB pathway in breast [135]
Akt	**Akt1** Akt1, eIF4B, H2B, HSP27, vimentin, YB-1, Wee1, PTP1B, PGC-1 alpha, PAR-4, p21, p27, mTor, Mdm2, lamin A/C, IRS1 [211] **Akt2** Substrates: Ask1, Ctnnb1, ER alpha, Ezrin, histone 3, IKK alpha, PGC-1 alpha and XIAP [211]	miR-302-367 cluster regulates AKT1 expression [138], while miR-612 was related to AKT2 repression [139]	Aberrant AKT signaling has been frequently documented in human cancers and appears to play a pivotal role in their progression [137]	Ectopic expression of miR-302-367 cluster in cervical carcinoma cells (HeLa and SiHa cells) inhibited cell proliferation and tumor formation [138]. Tao et al. [139] have shown that miR-612 inhibited hepatocellular carcinoma cells proliferation, migration, invasion, and metastasis through direct targeting AKT2.
mTOR	4E-BP1, Akt1, IRS-1, mTor, Myc, p70S6K, PTPN13, Stat3 and Ulk1 [212]	miR-99a [141,143] and miR-144 [144]	mTOR signaling is frequently deregulated in human cancers [142]	miR-99a was found to be downregulated in renal cell carcinoma (RCC) and its restoration suppressed RCC cell growth, migration and invasion, as well as induced cell cycle arrest *in vitro*. Besides, intratumoral delivery of miR-99a inhibited tumor growth in murine xenograft model of human RCC [143]

Table 1 (*continued*)

Kinase	Examples of substrates	Regulatory miRNAs	Protein data	Altered miRNA expression
Fyn	Abl, Bcr, CDK5, CTNNB1, Fyn, H3 histone, IRS1, LKB1, SHP2 [213]	miR-125a-3p [146]	Its overexpression is associated with several types of cancer, such as glioblastoma multiformae, squamous cell carcinoma of the head and neck, and melanoma [145]	Elevated levels of miR-125a-3p causes a dramatically decrease of Fyn expression [146]
Fak	Jak2, paxilin, integrin beta5, Stat1, Pten, Src, Fyn and IRS1 [214,215]	miR-7 [150] [149]	Increased FAK expression is frequently observed in human tumors and has been associated with an increased malignant phenotype and poor prognosis [148,149]	Overexpression of miR-7 in U87 and U251 glioblastoma cells inhibited their invasiveness and migration activity [150]. Besides, the overexpression of miR-7 in breast cancer cells suppressed proliferation, anchorage independent growth, three-dimensional growth in matrigel, migration and invasion (*in vitro* and *in vivo models* [149]
Pyk2	PTPN11, PTPN6, Src, Fyn, paxillin [214,215]		Highly activated in cancers [216]	Overexpression of miR-23b reduced PYK2 protein expression and significantly reduced glioma cell migration and invasion [151]. Ectopic expression of miR-517a and miR-517c inhibited HCC cells proliferation by blocking the G2/M transition [152]
Pak	aurora A, Bad, histone 3, Ilk, Mek1, Pak1, Raf and vimentin [153,154]. Substrates PAK2: Abl, ERK3, Jun, Mek1, Myc, Pak2 [153,154]	miR-7 targets PAK1 [157], miR-23b targets PAK2 [158] and miR-145 targets PAK4 [159]	PAKs have been related to cell transformation that results in tumor formation and cell invasiveness [153,154]	Overexpression of miR-7 in breast cancer cells inhibited motility, invasiveness, anchorage-independent growth and tumorigenic potential [157]
Rock	Ezrin, FAK, H3, IRS1, PTEN, radixin, vimentin, Rock2	miR-146a [161], miR-148b [162], miR-335 [163], miR-584 [164] and miR-1280 [165] was shown to target ROCK1, whereas miR-124 [166], miR-138 [167] and miR-139 [168] targeted ROCK2.	ROCK is frequently implicated in oncogenic transformation [160]	It was found a correlation between knockdown of ROCK kinases by the cited microRNAs and reduction of cell migration and invasion.
IGF1R	phospholipase C-gamma, mdm2, PTP1B, Src	miR-7 [171], miR-16 [172], miR-122 [173], miR-181b [174], miR-376a, miR-376c [175] and miR-497 [113,176]	Overexpressed in glioma patients [174], tongue squamous cell carcinoma cells [171], breast cancer [173], melanoma [175] and cervical carcinoma cells [176]	Shi et al. [174] have reported that miR-181b inhibited glioma proliferation, migration and invasion by targeting IGF1R and its downstream signaling pathways, PI3K/AKT and MAPK/ERK1/2. Ectopic expression of miR-7 in tongue squamous cell carcinoma (TSCC) cells reduced IGF1R expression and AKT activation, which in turn resulted in decreased cell proliferation and enhanced apoptosis [171]. miR-122, downregulated in breast cancer, also functions as a tumor suppressor *in vivo*, through targeting IGF1R and regulating PI3K/AKT/mTOR/p70S6K pathway [173]. In addition, miR-376a and miR-376c overexpression led to a significant decrease in melanoma cells migration by targeting IGF1R [175]. Luo et al. [176] have shown that ectopic expression of miR-497 in cervical carcinoma cells suppressed migration and invasiveness of these cells by

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Table 1 (*continued*)

Kinase	Examples of substrates	Regulatory miRNAs	Protein data	Altered miRNA expression
				post-transcriptionally targeting IGF1R
EGFR	Ago2, Crk, EGFR, Ezrin, Fak, PTP1B	miR-7 [179–181], miR-27a [182,183] and miR-133b [184]	EGFR signaling has emerged as a major therapeutic target in many cancers, since its deregulation have been associated to tumor cell proliferation, apoptosis resistance, invasion, angiogenesis and metastasis [179]	Ectopic expression of miR-7 decreased viability and invasiveness of primary glioblastoma lines [180]
Axl	phospholipase Cgamma1 (PLCgamma), p85alpha and p85beta subunits of phosphatidylinositol 3′-kinase (PI3-kinase), c-src, lck [217]	miR-34a and miR-199a/b	overexpression of AXL has been reported in several cancer types, such as colon, esophageal, thyroid, breast, lung, liver and astrocytoma-glioblastoma carcinomas [185]	Ectopic overexpression of these microRNAs decreased cell migration potential.
c-Met	c-Met, Fak, Shc1 [218,219]	miR-27a [182], miR-34a [191], miR-34c [192], miR-101 [193], miR-137 [194], miR-409-3p [195], miR-410 [196], miR-449a [197] and miR-7515 [198]	Deregulated in human cancers. The overexpression of c-MET and elevated levels of circulating HGF have been frequently detected in many cancers, and are associated with poor clinical outcomes [189]	

the cell cycle through phosphorylation and binding to activator proteins named cyclins [48]. The mammalian genome has twelve loci encoding CDKs, but only five of them (CDK1, CDK2, CDK3, CDK4 and CDK6) have been implicated in the regulation of cell cycle [49].

Cell cycle progression through the G1 phase is regulated by a complex mechanism involving CDK4, CDK6 and CDK2. Mitogenic signals result in increased transcription of D-type cyclins, which in turn form active complexes with CDK4 and CDK6. Then, these active kinases partially phosphorylate and inactivate the Retinoblastoma protein (pRb) allowing cyclin E synthesis. Cyclin E binds and activates CDK2, and the active complex CDK2-Cyclin E is responsible for further phosphorylation and inactivation of pRb [50]. Once phosphorylated, pRb releases E2F transcription factor allowing the transcription of genes necessary for entry into S phase [51]. CDK1 is activated by binding to A- or B-type cyclins and its activation is an essential step for mitotic entry through phosphorylation of numerous cytoplasmic and nuclear target proteins [49].

CDKs are frequently overactive in human cancers due to genetic and epigenetic alterations that affect their regulatory pathways. For this reason, CDKs have been considered as important targets for anticancer therapies [52]. Several miRNAs can influence cell cycle progression through targeting CDKs. Among them, miR-34 [53] and miR-195 [54] have been shown to target 3′UTR of CDK4. CDK6 was shown to be a direct target of miR-22 [55], miR-29 [56], miR-34 [57], miR-107 [58,59], miR-124a [60], miR-125b [61], miR-129 [62], miR-137 [63], miR-186 [64], miR-191 [65], miR-195 [66], miR-218 [67], miR-449a [68] and miR-494 [69]. Besides, CDK2 has been described as a target of miR-186 [64], miR-372 [70] and miR-885-5p [71], whereas CDK1 was found to be a target of miR-223 [72], miR-410 [73], miR-650[73], miR-1699, miR-1744 and miR-1798 [72].

3.1.2. Aurora kinases

Aurora kinases are conserved serine–threonine kinases that participate as key regulators of mammalian cell division. Aurora kinase B is a chromosomal passenger protein that participates in the spindle checkpoint and chromosome function. Besides, it has been related to the prevention of chromosome instability [74]. Therefore, aberrant expression of Aurora kinases can disturb checkpoint functions leading to genetic instability and cancer onset. The overexpression of Aurora kinases has been detected in several cancer types and correlates to a poor prognosis [75].

Two miRNAs were detected as regulators of Aurora kinase B expression, miR-24 [76] and let-7a [77]. The downregulation of let-7 has been detected as a common feature in several cancers, such as breast, colon, and lung cancers [78–80]. Liu et al. [77] showed that the level of let-7a is reduced in endometrial carcinoma cells, and the overexpression of this miRNA inhibited the growth of HeLa cells by targeting Aurora kinase B.

3.1.3. Cdc7 kinase

Cdc7 is a conserved serine/threonine kinase essential for the initiation of DNA replication [81,82]. Several studies have shown that Cdc7 participates in the response to DNA damage occurred during S-phase of the cell cycle [83–85], contributing to the maintenance of genomic stability. Because of that, it is expected that an altered control of Cdc7 could improve tumorigenesis. In fact, many reports have shown that Cdc7 is overexpressed in human cancer cell lines and many primary tumors [86]. In addition, it has been shown that the overexpression of Cdc7 enhances tumor cell survival by repairing stalled replication forks [87].

miR-29a was described as a regulator of Cdc7 expression by direct targeting 3′-UTR of this kinase and Cdc7 upregulation correlates with a downregulation of miR-29a [88]. miR-29a is downregulated in response to DNA damage induced by benzo[*a*]pyrene dihydrodiol epoxide (BPDE), a genotoxin present in cigarette smoke. Ectopic expression of miR-29a in lung cancer cells prevented Cdc7 accumulation in response to BPDE resulting in altered checkpoint signaling and increased cell death. Therefore, the loss of miR-29a might be a mechanism by which lung cancer cells acquire resistance to BPDE-induced DNA damage, allowing them to survive, proliferate and accumulate mutagenic lesions [88].

3.1.4. Polo-like kinases (PLKs)

PLKs comprise a highly conserved family of serine/threonine kinases involved in mitotic entry, centrosome maturation, spindle assembly and cytokinesis. PLK1 is the best-characterized member of this family and it is responsible for the phosphorylation of

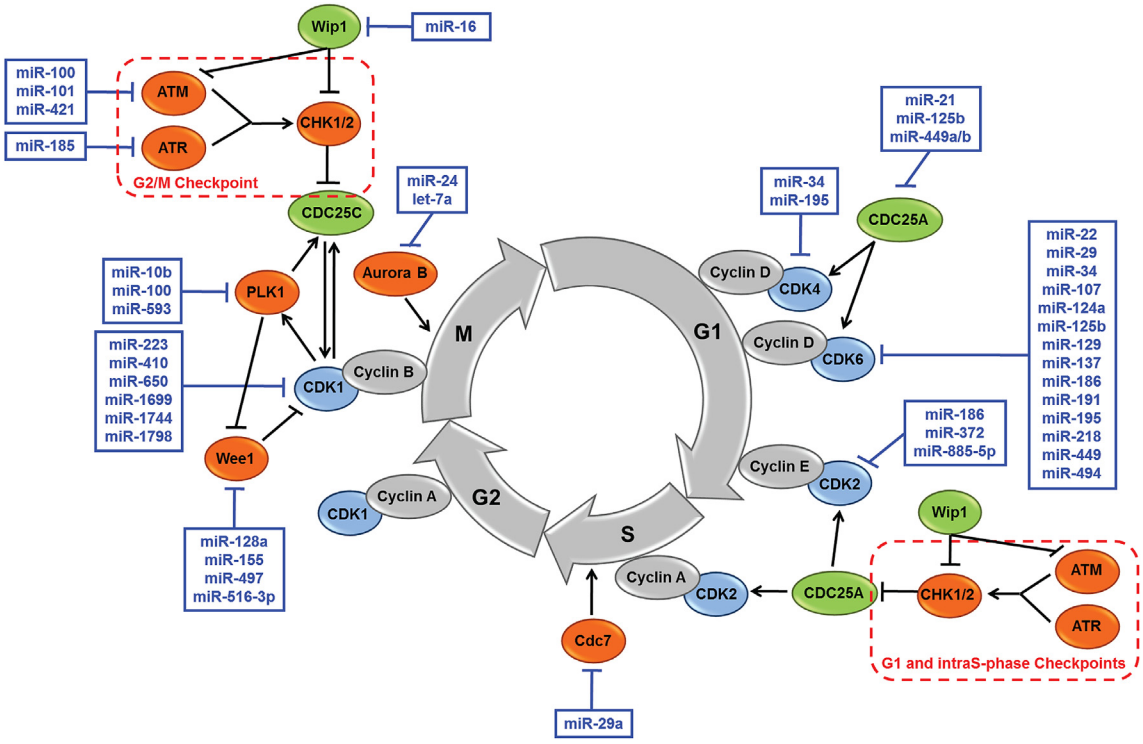

Fig. 3. Cell cycle control by miRNAs. Some interactions were omitted for clarity. The main protein kinases and phosphatases involved in the cell cycle control and discussed above are represented in the figure. miRNAs that control their expression are presented inside blue frames.

CDC25C, which in turn activates CDK1-Cyclin B complex inducing mitotic entry [89]. PLK1 is frequently overexpressed in cancers, including breast cancer [90], ovarian cancer [91], endometrial carcinomas [92], pancreatic cancer [93], renal carcinoma [94], colorectal cancer [95] and melanoma [96]. PLK1 overexpression contributes to oncogenesis not only by inducing proliferation, but also by promoting chromosome instability [97]. When PLK1 is inhibited tumor cells undergo mitotic arrest and apoptosis, besides promoting tumor growth inhibition *in vivo* [98–103].

MiR-10b [104], miR-100 [105,106] and miR-593 [107] have been proposed to target PLK1 mRNA. miR-10b was shown to be a master regulator of breast cancer cell proliferation and is downregulated in this cancer [104]. Ectopic expression of miR-10b decreased PLK1 expression and inhibited breast cell proliferation *in vitro* and tumor growth *in vivo* [104]. In naso-pharyngeal cancer cells, miR-100 was shown to be downregulated contributing to PLK1 overexpression and tumor progression [105]. In non-small cell lung cancer (NSCLC) miR-100 was also significantly downregulated, which was correlated with an advanced tumor stage, lymph node metastasis and reduced overall survival of patients [106]. NSCLC cells (A549) transfected with miR-100 mimics exhibited reduced PLK1 expression and underwent growth inhibition, G2/M cell cycle arrest and apoptosis [106]. miR-593, another miRNA that targets 3′UTR of PLK1, was shown to be less expressed in esophageal cancer (EC) cells [107]. The introduction of synthetic miR-593 in EC cells suppressed PLK1 expression, reduced cell proliferation and increased the number of cells in the G2/M phase [107].

3.1.5. *Wee1 kinase*

Wee1 is an evolutionarily conserved nuclear tyrosine kinase protein that prevents cell entry into mitosis by negatively modulating the cyclin B-CDK1 complex through phosphorylation of the amino acids Tyr15 and Thr14 of CDK1 [108]. Besides, it has been shown that Wee1 directly phosphorylates the mammalian core histone H2B at Tyr37 at the end of S phase, which is crucial for maintaining the correct histone-DNA stoichiometry prior to mitotic entry [109].

Wee1 has been identified as a direct target of miR-128a miR-155, miR-516a-3p [110] and miR-497 [111]. miR-128a, miR-155 and miR-516a-3p were shown to be overexpressed in nonfunctional pituitary adenomas [110]. Ectopic expression of these miRNAs in HeLa cells inhibited Wee1 expression, which was intriguingly accompanied by a decrease in cell proliferation [110].

miR-497 has been proposed to function as a tumor suppressor in several cancers [112,113], and its expression was shown to be reduced in neuroblastomas [111]. In addition, Wee1 was identified as a target of miR-497, and increased Wee1 expression was associated with poor prognosis of neuroblastoma. The siRNA knockdown of Wee1 in neuroblastoma cells increased apoptosis, while the overexpression of miR-497 reduced cell viability, increased apoptosis and sensitize neuroblastoma cells to treatment with cisplatin [111].

3.1.6. *Ataxia-Telangiectasia Mutated kinase (ATM) and ATM and Rad 3-related kinase (ATR)*

DNA Damage Checkpoint prevents cells from undergoing DNA replication or mitosis when DNA is damaged, providing an opportunity for DNA repair. In the presence of damaged DNA, a complex mechanism is triggered in mammalian cells to sense and transduce the signal to tumor suppressor pathways [48]. ATM and ATR are serine–threonine kinases members of PI3K superfamily that participates in sensing DNA damage. While ATM primarily responds to DNA double-strand breaks, caused by ionizing radiation and radiomimetic drugs, ATR also responds to damage caused by ultraviolet light and stalled replication forks [52]. These kinases phosphorylate CHK1 and CHK2, which in turn phosphorylate key proteins involved in DNA repair, cell cycle arrest and apoptosis. The major targets phosphorylated by CHKs are p53, responsible for cell

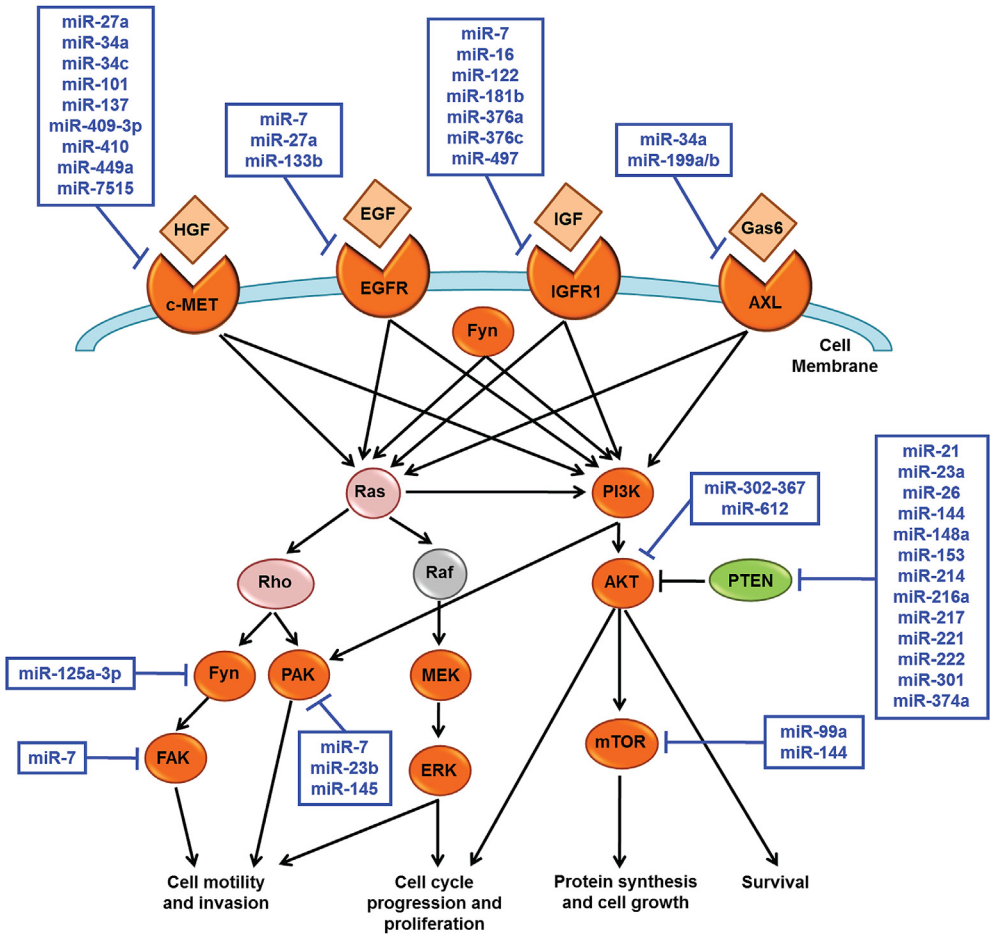

Fig. 4. Overview of the main signaling pathways controlled by tumor suppressor and oncogenic miRNAs. Some interactions were omitted for clarity. Inside blue frames are presented miRNAs that target kinases and phosphatases represented in the figure. After binding to specific ligands, the activated receptors c-MET, EGFR, IGF1R and AXL can activate key downstream pathways responsible for cell proliferation, growth, survival, motility and invasion. The major activated pathways include PI3K/AKT and MAPK/ERK. The kinase Fyn can be activated by RTKs and integrins and regulates PI3K/AKT, MAPK/ERK and also FAK signaling. PAK kinase can be activated by Rho GTPases, PI3K and integrins.

cycle arrest and apoptosis induction, and protein phosphatase CDC25, responsible for CDKs inhibition and cell cycle arrest [48,52].

ATM was previously identified as a target of miR-100 [114], miR-101 [115] and miR-421 [116]. The overexpression of miR-101 was shown to sensitize tumor cells to radiation *in vitro* and *in vivo* by targeting ATM [115]. The same effect of radiosensitization was shown for miR-100 overexpression in glioma cells [114]. Hu and colleagues [116] showed that HeLa cells overexpressing miR-421 were not able to block DNA synthesis in the S-phase of the cell cycle (S-phase checkpoint) in response to DNA damage. This effect was mediated by ATM downregulation and contributed to increase radiosensitivity in HeLa cells [116].

ATR has been recently identified as a target of miR-185 [117]. In renal cell carcinoma (RCC) tissues and cell line the expression of miR-185 was shown to be downregulated by ionizing radiation [117]. On the other hand, overexpression of miR-185 sensitized RCC cells to radiation both *in vitro* and *in vivo* [117].

3.2. Cell signaling kinases

3.2.1. Mammalian STE20-like protein kinase (MST) and large tumor suppressor kinase (LATS)

STE20 and LATS are key players in the Hippo signaling pathway, recently described as a new relevant pathway to cancer development [118,119]. The core of this pathway comprises two sets of serine/threonine kinases, MST1 (mammalian STE20-like protein kinase 1) and MST2, and the LATS1 (large tumor suppressor 1) and LATS2, together with the adaptor proteins SAV1, MOB1A (MOB kinase activator 1A) and MOB1B. Upon activation by stimuli such as cell–cell contact, the Hippo pathway kinase cascade phosphorylates the oncoproteins YAP (Yes-associated protein) and TAZ (co-activator with PDZ-binding motif). The phosphorylation of YAP/TAZ inhibits their activity and stimulates their ubiquitination and degradation. When dephosphorylated YAP/TAZ migrate to the nucleus, and modulate the activity of transcription factors such as TEADs and SMADs, thereby inducing cell proliferation and reducing apoptosis [118,119].

MST2 was shown to be downregulated by miR-133b which was found to be overexpressed in human cervical carcinomas [120]. Using the luciferase reporter assay, Qin and colleagues [120] confirmed 3′UTR of MST2 as a direct target of miR-133b. The silencing of MST2 in epidermoid cervical carcinoma (CaSki) cells using a specific siRNA enhanced cell proliferation and increased the number of colonies formed in soft agar.

LATS2, classically identified as a downstream target of MST2 on the Hippo pathway, act as a tumor suppressor through modulating different processes such as cell proliferation and cell death ([121–123]. The hypermethylation of LATS2 gene and consequently, a reduction in LATS2 expression has been frequently reported in different cancers [124–126], and is related to a more aggressive tumor phenotype. Some studies have identified LATS2 mRNA as a direct target of miR-31 [127], miR-372 [128,129] and miR-373

[128,130]. miR-31 was found to be overexpressed in murine and human lung cancers cells, and the knockdown of miR-31 increased LATS2 expression and repressed growth and tumorigenicity of these cells [127]. In human gastric cancer (AGS) cells the inhibition of miR-372 using antisense miR-372 oligonucleotide increased LATS2 expression, induced cell cycle arrest, suppressed proliferation and increased apoptosis of these cells [129]. The downregulation of LATS2 by miR-373 was first described by Voorhoeve and colleagues [128] in testicular germ cell tumors, and afterward the same interaction was proposed by Lee and colleagues [130] in esophageal cancer cell lines. In esophageal squamous cell carcinomas the level of LATS2 protein expression is inversely correlated with miR-373 expression [130].

3.2.2. BCR-ABL1 kinase

BCR-ABL oncoprotein, a non-receptor tyrosine kinase, is expressed from the Philadelphia chromosome upon the t(9;22)(q34;q11) chromosomal translocation and it is considered as the hallmark in chronic myelogenous leukemia (CML). BCR-ABL1 is a direct target of the miRNA miR-203. It is silenced by genetic and epigenetic mechanisms in CML, resulting in the overexpression of ABL1 and BCR-ABL1, while restoration of miR-203 expression reduces ABL1 and BCR-ABL1 expression and inhibits cell proliferation [131]. More recently, it was shown that miR-29b [132] and miR-30a [133] targeted BCR-ABL1 and promoted its downregulation in bone marrow from CML patients. In K562 leukemia cells, the overexpression of miR-29b inhibited cell growth, colony formation ability and induced apoptosis [132]. Similarly, the overexpression of miR-30a in K562 leukemia cells reduced ABL1 and BCR-ABL1 protein expression, proliferation, and blocked cell cycle progression between G1 and S [133].

3.2.3. PKCε kinase

PKCε is an isoform that belongs to the novel PKC subfamily, which lacks the calcium binding domain and is regulated by diacylglycerol [134]. In breast cancer cell lines the downregulation of PKCε caused inhibition of NFκB signaling, augmented apoptosis, and increased sensitivity toward ionizing radiation and treatment with chemotherapeutics [134]. In breast cancer it was also found that enhanced expression of miR-31 provokes an inhibition of the oncogenic NFκB pathway, and miR-31 directly targets PRKCE, the gene that encodes PKCε [135].

3.2.4. PI3K-AKT-mTOR pathway

AKT is a serine/threonine kinase downstream of phosphoinositide 3-kinase (PI3K) pathway. Activated AKT stimulates numerous processes, including cell cycle progression, survival, metabolism and migration through phosphorylation of many substrates, including mammalian target of rapamycin (mTOR) [136]. Aberrant AKT signaling has been frequently documented in human cancers and appears to play a pivotal role in their progression [137]. Previous reports have identified the miR-302-367 cluster as a regulator of AKT1 expression [138], while miR-612 was related to AKT2 repression [139]. Through direct targeting AKT1 and cyclin D1, the ectopic expression of miR-302-367 cluster in cervical carcinoma cells (HeLa and SiHa cells) inhibited cell proliferation and tumor formation [138]. Tao et al. [139] have shown that miR-612 inhibited hepatocellular carcinoma cells proliferation, migration, invasion, and metastasis through direct targeting AKT2.

mTOR controls different biological processes including protein and lipid biosynthesis, energy metabolism, autophagy, cell survival, and cytoskeletal organization [140,141]. mTOR signaling is frequently deregulated in human cancers [142]. miR-99a [141,143] and miR-144 [144] have been shown to effectively downregulated mTOR expression by direct binding the 3′UTR of its mRNA. miR-99a was found to be downregulated in renal cell carcinoma (RCC) and its restoration suppressed RCC cell growth, migration and invasion, as well as induced cell cycle arrest *in vitro*. Besides, intratumoral delivery of miR-99a inhibited tumor growth in murine xenograft model of human RCC [143].

3.2.5. Cytoskeleton regulators

In this Section 4 kinases that display an important role in cytoskeleton dynamics will be discussed.

Fyn is a non-receptor tyrosine kinase belonging to the Src family kinase and has a critical role in cell adhesion, proliferation, migration, and survival. Its overexpression is associated with several types of cancer, such as glioblastoma multiformae, squamous cell carcinoma of the head and neck, and melanoma [145]. Recently, Ninio-Many et al. [146] have shown that Fyn expression is dramatically reduced by elevated levels of miR-125a-3p. Besides, the activity of proteins downstream of Fyn, such as FAK, paxillin, and AKT, was also dropped and the cellular response was cell cycle arrest at the G2/M phases and migration blockage.

Focal adhesion kinase (FAK) is the prototype for a family of non-receptor tyrosine kinases. While FAK is ubiquitously expressed, a second member of this family, referred as PYK2, has a more restricted expression [147]. FAK is an important mediator of integrin signaling and is related to cellular processes such as cell motility, cell proliferation, and cell survival. Increased FAK expression is frequently observed in human tumors and has been associated with an increased malignant phenotype and poor prognosis [148,149]. FAK and PYK2 have been described as targets for some miRNAs. MiR-7 was shown to target FAK in glioblastoma cells [150] and breast cancer cells [149]. The overexpression of miR-7 in U87 and U251 glioblastoma cells inhibited their invasiveness and migration activity [150]. miR-7 expression was shown to be decreased in malignant versus normal breast tissue. The overexpression of miR-7 in breast cancer cells suppressed proliferation, anchorage independent growth, three-dimensional growth in matrigel, migration and invasion. Besides, miR-7 overexpression inhibited primary breast tumor development, local invasion, and metastasis of breast cancer xenografts [149]. PYK2 was found to be a target of miR-23b [151], miR-517a, and miR-517c [152]. Overexpression of miR-23b reduced PYK2 protein expression and significantly reduced glioma cell migration and invasion [151]. The expression of miR-517a and miR-517c was reduced in hepatocellular carcinoma (HCC) samples. Through PYK2 regulation, ectopic expression of miR-517a and miR-517c inhibited HCC cells proliferation by blocking the G2/M transition [152].

P21 activated kinases (PAKs) are serine/threonine kinases that function as important regulators of cytoskeletal dynamics and cell motility, but have also been implicated in controlling death and survival signaling and promoting cell proliferation. Consequently, PAKs have been related to cell transformation that results in tumor formation and cell invasiveness [153,154]. PAK1 expression is widely upregulated in breast tumors and correlates with tumor invasiveness and cyclin D1 expression [155]. PAK4 was found overexpressed in cell lines derived from different human cancers types, and this finding was also related to increased tumorigenesis [156]. In breast cancer cells, 3′UTR of PAK1 mRNA was targeted by miR-7, and the introduction of miR-7 in these cells inhibited motility, invasiveness, anchorage-independent growth and tumorigenic potential [157]. PAK2 was shown to be a direct target of miR-23b in breast cancer [158], whereas miR-145 was found to be a regulator of PAK4 expression in human colon cancer cells [159]. Wang et al. [159] showed that miR-145 is downregulated in human colon cancer cells, and restoration of miR-145 in SW620 cells attenuated cell growth *in vitro*. Additionally, the findings

demonstrated that miR-145 downregulates p-ERK expression by targeting PAK4, which leads to inhibition of tumor growth.

The Rho GTPase family has a key role in regulating actin cytoskeleton organization and dynamics. RhoA and RhoC family members act primarily through two serine/threonine kinases (ROCK1 and ROCK2) that mediate the phosphorylation of numerous downstream target proteins. ROCK kinases influence several processes such as cell morphology regulation, cell adhesion, cell motility, proliferation, differentiation, and apoptosis. Rho/ROCK pathway has been frequently implicated in oncogenic transformation [160]. Several miRNAs have been described as regulators of ROCK kinases expression. Among them, miR-146a [161], miR-148b [162], miR-335 [163], miR-584 [164] and miR-1280 [165] was shown to target ROCK1, whereas miR-124 [166], miR-138 [167] and miR-139 [168] targeted ROCK2. In a general, there is a correlation between knockdown of ROCK kinases by the cited miRNAs and reduction of cell migration and invasion.

3.3. Kinase receptors

3.3.1. Insulin-like growth factor I receptor (IGF1R)

IGF1R is a tyrosine kinase receptor that is mainly activated by IGF1 and IGF2. IGF1R activates multiple downstream signaling cascades (PI3K/AKT and MAPK/ERK) involved in cell proliferation, differentiation, and survival [169,170]. Several miRNAs have been pointed out as modulators of IGF1R expression, such as miR-7 [171], miR-16 [172], miR-122 [173], miR-181b [174], miR-376a, miR-376c [175] and miR-497 [113,176].

Shi et al. [174] have reported that miR-181b inhibited glioma proliferation, migration and invasion by targeting IGF1R and its downstream signaling pathways, PI3K/AKT and MAPK/ERK1/2. IGF1R was overexpressed in glioma patients, and its protein levels were inversely correlated with miR-181b expression. Chen et al. [172] have reported that miR-16 is downregulated in osteosarcoma cell lines and tissues. The overexpression of miR-16 suppresses osteosarcoma cell proliferation and tumor growth in nude mice by inhibiting Raf1-MEK1/2-ERK1/2 pathway [172]. Additionally, ectopic expression of miR-7 in tongue squamous cell carcinoma (TSCC) cells reduced IGF1R expression and AKT activation, which in turn resulted in decreased cell proliferation and enhanced apoptosis [171]. miR-122, downregulated in breast cancer, also functions as a tumor suppressor *in vivo*, through targeting IGF1R and regulating PI3K/AKT/mTOR/p70S6K pathway [173]. In addition, miR-376a and miR-376c overexpression led to a significant decrease in melanoma cells migration by targeting IGF1R [175]. Luo et al. [176] supported a similar idea, showing that ectopic expression of miR-497 in cervical carcinoma cells suppressed migration and invasiveness of these cells by post-transcriptionally targeting IGF1R.

3.3.2. Epidermal growth factor receptor (EGFR)

EGFR is a member of the ErbB receptor tyrosine kinase family. Several signaling pathways are downstream targets of EGFR, such as PI3K/AKT [177] and Ras/Raf/ERK1/2 pathways [178]. For this reason, EGFR signaling has emerged as a major therapeutic target in many cancers, since its deregulation have been associated to tumor cell proliferation, apoptosis resistance, invasion, angiogenesis and metastasis [179]. Some miRNAs have been shown to directly target EGFR and, hence, have been considered potential therapeutic tools for cancer treatment. Among them are miR-7 [179–181], miR-27a [182,183] and miR-133b [184].

3.3.3. AXL

Tyro3-Axl-Mer (TAM) receptor tyrosine kinase subfamily (RTKs) comprises Tyro-3 (also called Sky), MER, and AXL. Signaling pathways activated by AXL include PI3K and ERK. The overexpression of AXL has been reported in several cancer types, such as colon, esophageal, thyroid, breast, lung, liver and astrocytoma-glioblastoma carcinomas [185]. Increased AXL expression has been associated with improved cell survival, proliferation, migration, invasion, angiogenesis and metastasis [186].

AXL was recently described as a direct target of miR-34a [186,187] and miR-199a/b [186]. The major effect promoted by ectopic overexpression of these miRNAs was the decreased cell migration potential.

3.3.4. c-MET

c-MET belongs to a subfamily of RTKs, which also includes RON and SEA [188]. Hepatocyte growth factor (HGF) is the unique ligand for c-MET. After activation by HGF binding, c-MET autophosphorylates, recruits adaptor proteins and activates multiple downstream effectors. c-MET potentially activates some signaling pathways as RAS-MAPK (mitogen-activated protein kinase), PI3K, AKT, and STAT3/5 (signal transducer and activator of transcription 3/5). As a consequence, activated c-MET regulates a variety of cellular processes, including proliferation, survival, adhesion, motility and invasion [189].

The c-MET/HGF pathway is one of the most commonly deregulated pathways in human cancers. In fact, the overexpression of c-MET and elevated levels of circulating HGF have been frequently detected in many cancers, and are associated with poor clinical outcomes [189]. Different studies have shown that the downregulation or inhibition of HGF/c-MET results in reduced cell growth, survival, migration and invasion *in vitro*, and decreased tumorigenic and metastatic potential *in vivo* [189,190]. Recently, a variety of miRNAs were shown to target c-MET in cancer cells, contributing to reduce their tumorigenic potential. Among them are miR-27a [182], miR-34a [191], miR-34c [192], miR-101 [193], miR-137 [194], miR-409-3p [195], miR-410 [196], miR-449a [197] and miR-7515 [198].

4. Modulation of protein phosphatases by miRNAs

Protein phosphatases are not as widely encoded in the human genome as their counterpart protein kinases. However, despite having relatively few genes encoding catalytic subunits of protein phosphatases, some of them have different regulatory subunits that, combined with the catalytic subunit, allow translocation and binding to specific targets [220].

MiRNAs can also regulate protein phosphatase expression, either by targeting the regulatory or the catalytic subunit, leading to hallmarks of tumor cells (unrestricted cell proliferation, resistance to apoptosis, and an improved ability of migration and invasion). We will describe below seven protein phosphatases that have established connections to cancer. Additional information can be found in Table 2, while some of the discussed phosphatases are also present in Figs. 3 and 4, which summarize signaling pathways and cellular responses these proteins take part in.

4.1. Cell division cycle 25 (CDC25)

CDC25 is a group of highly conserved dual-specificity phosphatases. In mammals there are three different CDC25 homologs: CDC25A, B and C. All three stimulate cell cycle progression, since they dephosphorylate the inhibitory site of CDK, and, in turn, activate cyclin/CDK complexes [221,222]. Therefore, abnormal expression of those phosphatases has been observed in a number of tumors [223–229].

CDC25A is the major regulator of G1/S transition and S phase progression, while CDC25B contributes to G2 progression and CDC25C is restricted to mitosis [230]. CDC25A is overexpressed in a variety of human cancers [231], which is related to aberrant

Table 2
Regulation of protein phosphatases by miRNAs in cancer.

Protein	Examples of substrates	Regulatory miRNAs	Protein data	Altered miRNA expression
CDC25	CDK1 [279], CDK2 [279], p53 [280]	miR-21 [233], miR-125b [61], miR-449a [68,232] and miR-449b [68]	Highly expressed in cancer cells [231]	Overexpression leads to reduced cell proliferation and growth [61,232–235]
PTEN	Phosphatidylinositol 3,4,5-trisphosphate. Indirectly inhibits AKT [202]	miR-21, miR-23a, miR-26, miR-144 [237], miR-148a, miR-153 [238], miR-214 [239], miR-216a and miR-217 [240], miR-221 [241], miR-222 [242], miR-301 [243] as well as miR-374a [244]	Tumor suppressor. The gene is mutated in several cancers [236]	Overexpression is associated to cancer cell survival, migration, growth and proliferation [245–256]
PTPN9	N/A	miR-24 [258]	Reduced expression in cancer cells [258]	N/A
PRL1	N/A	miR-339-5p [259]	Overexpressed in cancer cells. Stimulates progression in the cell cycle [281,282]	Overexpression leads to inhibition of cell growth and reduced migration and invasion in colorectal cancer cells. It also suppressed tumor growth *in vivo* [259]
PP6	TAK1 [283]	miR-373 [260]	Negative cell cycle regulator [284]	Overexpression promotes cell proliferation of hepatocellular carcinoma cell lines [260]
PTPN1	Insulin receptor [285], BCR [286], Src [287], PDGFR [288]	miR-362-3p [263]	Both tumor suppressor and tumor promoter [261]. Leads to proliferation and metastasis in colon cancer and breast cancer cells [262,263]	Overexpression is associated with reduced risk of recurrence in adenocarcinoma patients [263]
PPM1D	ATM [267], CHK1 [265], p53 [265], CHK2 [266]	miR-16 [275]	Regulator of DNA damage signaling pathways, frequently overexpressed in many human cancers [264]	Overexpression suppressed the growth of mouse mammary tumor stem cells and ensitized MCF-7 human breast cancer cells to doxorubicin [275]

progression through G1/S and increased proliferation. miR-125b [61], miR-449a [68,232] and miR-449b [68] are all regulators of CDC25A expression. The expression of all these miRNAs was found to be reduced in cancer cells, which was related to CDC25A overexpression. miR-21, despite targeting many tumor suppressor proteins, also targets CDC25A [233].

The overexpression of miR-125b in U251 glioma stem cells decreased CDC25A expression and cell proliferation through cell cycle arrest at G1 phase [61]. Besides, the restoration of miR-449a in human bladder cancer cells inhibited cell growth and induced G1 phase arrest through downregulation of CDC25A and CDK6 [232]. Together, these results demonstrate the importance of controlling CDC25A expression to achieve tumor suppression.

Liffers et al. [234] have shown for the first time a downregulation of CDC25B by miR-148a. They showed that miR-148a exhibited a significant 4-fold downregulation in human pancreatic ductal adenocarcinoma (PDAC) in comparison to normal pancreatic ductal cells. The same authors also reported that the overexpression of miR-148a in the pancreatic cancer cell line IMIM-PC2 inhibited tumor cell growth and colony formation. CDC25B was identified as a potential target of miR-148a by *in silico* analysis using PicTar, Targetscan and miRanda together with Gene Ontology. Accordingly, the activity of a luciferase reporter containing the 3′UTR of CDC25B was repressed in the presence of miR-148a mimics, confirming that miR-148a targets the 3′UTR of CDC25B. Yu et al. [235] have observed that miR-141 is significantly downregulated in renal cell carcinoma and, by using miRNA target prediction software, they found that miR-141 could target the 3′UTR sequence of CDC25B. When miR-141 expression was restored in renal cell carcinoma the proliferation rate of those cells was suppressed and the endogenous CDC25B protein levels dropped. In addition, the authors suggested that the transcriptional loss of miR-141 and the resultant increase in CDC25B expression facilitates increased genomic instability at an early stage of renal cell carcinoma development.

4.2. Phosphatase and tensin homolog (PTEN)

PTEN is a dual-specificity phosphatase and well-known tumor suppressor gene. As a lipid phosphatase, PTEN dephosphorylates phosphatidylinositol 3,4,5-trisphosphate (PIP3) to phosphatidylinositol 3,4,5-diphosphate (PIP2), thereby inhibiting AKT, a key kinase that mediates proliferation and cell survival [236]. Several miRNAs, including miR-21, miR-23a, miR-26, miR-144 [237], miR-148a, miR-153 [238], miR-214 [239], miR-216a and miR-217 [240], miR-221 [241], miR-222 [242], miR-301 [243], and miR-374a [244] have been established as regulators of PTEN expression.

miR-21 was one of the first miRNAs detected in the human genome, and is also known to be up-regulated in many types of human malignancies [245]. It has been shown that several tumor suppressors including PTEN [246], tumor suppressor gene tropomyosin 1 (TPM1) [247], programmed cell death 4 (PDCD4) [248], maspin [249], and matrix metalloproteinases inhibitors RECK and TIMP3 [250] are targets of miR-21, suggesting that miR-21 is an important oncogenic miRNA closely related to tumor growth and metastasis.

Gliomas are the most common and deadly type of primary brain tumor. cAMP response element-binding protein (CREB), a proto-oncogenic transcription factor that is overexpressed in gliomas and is able to promote gliomagenesis by modulating the expression of mir-23a, which targets the tumor suppressor PTEN [251]. miR-26 can also enhance gliomagenesis by affecting PTEN levels [252].

miR-148a stimulated cell survival, cell migration, anchorage independent cell growth and tumorigenesis in SCID by targeting PTEN [253].

PTEN is downregulated by miR-214 in ovarian cancer [254]. In addition, miR-216a and miR-217, both of which target PTEN, activate AKT through PTEN down-regulation in kidney disorders [255].

miR-221 and miR-222 had an increase of expression in HCT116 and HKe3 cells (HCT116 cells in which mutated *KRAS* allele was deleted) in 3D culture. These miRNAs were regulated by oncogenic *KRAS* and were significantly overexpressed in human colorectal tumor specimens. Importantly, both miRNAs target PTEN [256].

miR-301 overexpression has been implicated as a negative prognostic indicator in lymph node negative invasive ductal breast cancer. By using luciferase reporter assay, PTEN was identified as a target of miR-301 [243].

miR-374a is markedly upregulated in primary tumor samples from patients with distant metastases and was associated with poor metastasis-free survival. This miR directly targets and

suppresses multiple negative regulators of the Wnt/β-catenin signaling cascade, including PTEN [244].

4.3. Tyrosine-protein phosphatase non-receptor type 9 (PTPN9)

Tyrosine-protein phosphatase non-receptor type 9 (also called PTP-MEG2) is encoded by the *PTPN9* gene, in human. PTPN9 inhibits receptor PTK activation by direct dephosphorylation of EGFR and ErbB2 [257].

Du et al. [258] have observed that miR-24-expressing cells and tumors displayed higher levels of phosphorylated EGFR, whereas expression of the phosphatases PTPN9 and receptor-type tyrosine-protein phosphatase F (PTPRF) were repressed. Those authors confirmed that miR-24 directly targets both PTPN9 and PTPRF. Besides, they observed that the amount of phosphorylated EGFR was much higher in patients with metastatic breast carcinoma whereas levels of PTPN9 and PTPRF were lower.

4.4. Phosphatase of regenerating liver (PRL)

PRL is a group of protein tyrosine phosphatases consisting of three members, PRL-1, -2, and -3. There is an inverse correlation between miR-339-5p and PRL-1 expressions. Zhou et al. [259] found downregulated miR-339-5p levels in colorectal cancer tissues and highly invasive CRC cell lines. Furthermore, overexpression of miR-339-5p in CRC leads to inhibition of cell growth, migration and invasion. It also suppressed tumor growth *in vivo*. Overexpression of miR-339-5p also reduces the expression of PRL-1 mRNA and protein, which was associated with low expression of phosphorylated-extracellular signal-regulated kinase 1/2 (p-ERK1/2). miR-339-5p acts as a tumor suppressor and plays a role in metastasis and inhibition of cellular growth as demonstrated in CRC cells via targeting PRL-1 and regulating p-ERK1/2.

4.5. Protein phosphatase 6 (PP6)

PP6 is a serine/threonine protein phosphatase classified as a type 2A phosphatase family member based on its sequence homology to the catalytic subunit of PP2A. Wu et al. [260] found that miR-373 is upregulated in human hepatocellular carcinoma (HCC) tissues as compared with adjacent normal tissues, and promotes the proliferation of the HCC cell lines HepG2 and QGY-7703 by regulating the cell cycle progression from G1 to S-phase. These authors detected the gene encoding the protein phosphatase 6 catalytic subunit (PPP6C), a negative cell cycle regulator, as a direct target gene of miR-373. Accordingly, overexpression of PPP6C abolished the regulation of cell cycle and cell growth exercised by miR-373 in HepG2 cells.

4.6. Protein-tyrosine phosphatase non-receptor type 1 (PTPN1 or PTB1B)

Protein-tyrosine phosphatase non-receptor type 1 (PTPN1 or PTP1B) has, over the last decade, attracted great attention due to its role in leptin and insulin metabolism and, more recently, in cancer [261]. Increased levels of PTPN1 have been shown to promote tumorigenicity of colon cancer cells by the activation of Src [262]. In breast cancer PTPN1 activity is required for efficient invadopodia formation and breast cancer invasion. Christensen et al. [263] have reported that high miR-362-3p expression in adenocarcinomas was found to be associated with reduced risk of recurrence in two independent patient cohorts. Functional characterization of miR-362-3p demonstrated that this miRNA inhibits proliferation. miR-362-3p transfection into colon cancer cell lines decreased among others the amount of PTPN1, which was identified as direct miR-362-3p targets.

4.7. Wild-type p53-induced phosphatase 1 (Wip1 or PPM1D)

Wip1 is a serine/threonine phosphatase that has a critical role as regulator of DNA damage signaling pathways [264]. Wip1 dephosphorylates several DNA damage-responsive proteins, such as ATM, CHK1, and CHK2 [265–267], reverting DNA damage-induced cell cycle checkpoint. Thus, Wip1 releases cells from the cell cycle arrest induced by DNA damage, allowing them to progress through the cell cycle. PPM1D is an oncogene frequently amplified in human tumors, which results in Wip1 overexpression in many different cancer types, including breast carcinomas, ovarian adenocarcinomas, neuroblastomas, pancreatic adenocarcinomas, gastric carcinomas, and medulloblastomas [268–274]. miR-16 was previously identified as a repressor of Wip1 expression [275]. After DNA damage, miR-16 is immediately induced, which in turn delays the increase in Wip1 expression. This effect prevents a premature inactivation of ATM/ATR signaling and allows DNA damage repair. miR-16 was found downregulated in mammary tumor stem cells. Its overexpression suppressed the growth of mouse mammary tumor stem cells and sensitized MCF-7 human breast cancer cells to treatment with doxorubicin [275].

4.8. Src homology-2 domain-containing inositol 5-phosphatase 1 (SHIP1)

SHIP1 hydrolyzes the 5′ phosphate from phosphatidylinositol (3,4,5)-triphosphate and inositol-1,3,4,5-tetrakisphosphate, affecting multiple signaling pathways. SHIP1 expression is restricted to hematopoietic cells where it negatively regulates myeloid cell proliferation and survival. O'Connell and collaborators [276] identified SHIP1 as a direct target of miR-155. Ectopic expression of miR-155 resulted in a myeloproliferative disorder. Besides, it was reported that in diffuse large B cell lymphoma high levels of miR-155 are associated with diminished SHIP1 expression [277]. Furthermore, transfection of a myeloid cell line with miR-210 resulted in loss of SHIP-1 protein expression [278].

5. Final considerations

We have drawn a picture of the important role miRNAs exert on regulating protein kinase and protein phosphatase expression and the effects this regulation has, or may have, in the control of cell growth, survival, proliferation, adhesion, and every other cancer-related signaling pathway. The antagonistic nature of protein kinases and protein phosphatases ensures that the knowledge of their expression and their activities is critical for the understanding of oncogenic processes. Besides, we do believe that the identification of miRNAs that target protein phosphatases and *vice versa* will open a new avenue to understanding the role of this enzyme family in cancer biology, since during the last few decades there a huge amount of information about kinases has been released but the same cannot be said for phosphatases.

Not all miRNAs regulating phosphatases and kinases, however, act through straightforward processes. The complexity of the phosphatase (but also other enzymes, such as kinases) specificity mechanism, with few catalytic subunits combined to an array of regulatory subunits, warrants a tangled regulatory network that may seem ambiguous at first look. Therefore, studies that address how microRNAs interfere in feedback loops and protein interactions in pathways formed by protein kinases and phosphatases are the next step towards understanding regulatory mechanisms that trigger the induction and development of

malignant transformations. In addition, it is important to keep in mind the complexity of miRNA action, mainly regarding multiple targets for a given miRNA, which makes the action of miRNAs dependent on cell type, metabolic context and target mRNAs that are expressed. Besides, miRNAs do not act in isolation, which is why it is essential to have an overview of the context at the miRNome, transcriptome and proteome levels in order to assess the metabolic network as a whole rather than a unique target mRNA or pathway. In addition, just to give an idea about how complex this process can be, it has become clear that some miRNAs target both oncogenic and tumor suppressor proteins. This is the case of miR-21, miR-29 and the miR-17-92 cluster [289–291].

In relation to the application of miRNAs, there are some recent reviews that comprehensively covered this subject. In general, it has been reported that miRNAs have great potential in the diagnosis, prognosis and cancer therapy [292–294]. For instance, miR-21 has been considered as a biomarker for diagnostic and prognostic assessments, as elevated blood levels of miR-21 were observed to be correlated with resistance of pancreatic and lung cancer [295,296]. More recently, Manceau and collaborators [297] reported that the expression of miR-31-3p can be used to identify patients with wild-type *KRAS* metastatic colorectal cancer who are good responders to anti-EGFR therapy. Concerning treatment, miR-34 is one of the first candidates for targeted cancer therapy. Systemic delivery of miR-34 caused a decrease in a murine model of lung cancer [298]. Despite the great potential of miRNAs as therapeutic agents, there are some challenges in using them clinically: a) development of efficient systems for delivering miR or anti-miR *in vivo* and consequently improving the biological effect and minimizing off-targets; b) understanding the miRNA network *in vivo* and be able to predict toxicity.

Conflict of interest

The authors declare no conflict of interest.

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