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Review

MicroRNAs and the cell cycle

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ABSTRACT

The control of cell proliferation by microRNAs (miRNAs) is well established and the alteration of these small, non-coding RNAs may contribute to tumor development by perturbing critical cell cycle regulators. Oncogenic miRNAs may facilitate cell cycle entry and progression by targeting CDK inhibitors or transcriptional repressors of the retinoblastoma family. On the other hand, tumor suppressor miRNAs induce cell cycle arrest by downregulating multiple components of the cell cycle machinery. Recent data also suggest that miRNAs act co-ordinately with transcriptional factors involved in cell cycle regulation such as c-MYC, E2F or p53. These miRNAs not only can potentiate the function of these factors but they may also limit the excessive translation of cell cycle proteins upon mitogenic or oncogenic stimuli to protect cells from replicative stress. The implications of these regulatory networks in cell proliferation and human disease are discussed.

1. Introduction

The cell division cycle is regulated through multiple molecular pathways and checkpoints. Most adult mammalian cells are quiescent (i.e. out of the cell cycle) and re-entry into the cell cycle requires the inactivation of the retinoblastoma protein (pRB) and the transcription of genes required for DNA replication during S (for DNA *S*ynthesis) phase or chromosome segregation during mitosis (M phase) [1]. Most mitogenic pathways result in the transcriptional induction of D-type cyclins and the subsequent activation of cyclin-dependent kinases (CDKs) such as CDK4 and CDK6 (Fig. 1). These kinases, as well as other family members, phosphorylate and inactivate pRB, a transcriptional repressor that inhibit E2F transcription factors and recruit chromatin remodeling complexes that lead to the repression of targeted genes [1]. Upon mitogenic stimuli, the active CDK4/6-cyclin D complexes inactivate pRB, leading to the E2F-dependent transcription of cell cycle genes. Once the DNA replication machinery is expressed, cells are committed to S-phase and progression throughout the cell cycle is monitored by a variety of checkpoints that are able to arrest or delay the cell cycle in the presence of DNA damage, defective replication or mitotic aberrancies. For instance, a variety of anti-proliferative signals leads to the expression of several CDK inhibitors, such as the members of the INK4 ($p16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$ or $p19^{INK4d}$) or Cip/Kip ($p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$) families [1,2].

Once the genome is replicated during S-phase, cells are ready to segregate the two genomes into two daughter cells during mitosis. Since most proteins required for mitosis have been synthesized in the earlier phases of the cell cycle, the regulation of the G2/M transition and mitotic exit mostly depends on post-translational mechanisms. CDK1, when bound to A- or B-type cyclins, is a major kinase required for mitotic entry through the phosphorylation of a significant number of cytoplasmic and nuclear substrates [3]. Other kinases required for the duplication and maturation of centrosomes include members of the Polo-like kinases (PLK) and Aurora kinases [4]. These proteins, as well as many other regulators involved in the cytoplasmic and nuclear changes required for mitosis, control the establishment of a bipolar spindle and the orderly segregation of chromosomes into the two daughter cells. Mitotic exit (i.e. reformation of two interphasic nuclei) requires the elimination of a significant number of cell cycle regulators by proteolysis. This is mediated at least partially by the Anaphase-promoting complex (APC/C), an E3 ubiquitin ligase that targets multiple cell cycle proteins with ubiquitin for proteasome-dependent degradation [5,6].

Since cell cycle progression requires the presence and activity of multiple proteins that are not expressed in quiescent cell, the regulation of the levels of these proteins is a central issue in the understanding of the control of the cell cycle and its deregulation in human disease. For instance, genetic mutations leading to the overexpression of cyclins or the elimination of several CDK inhibitors

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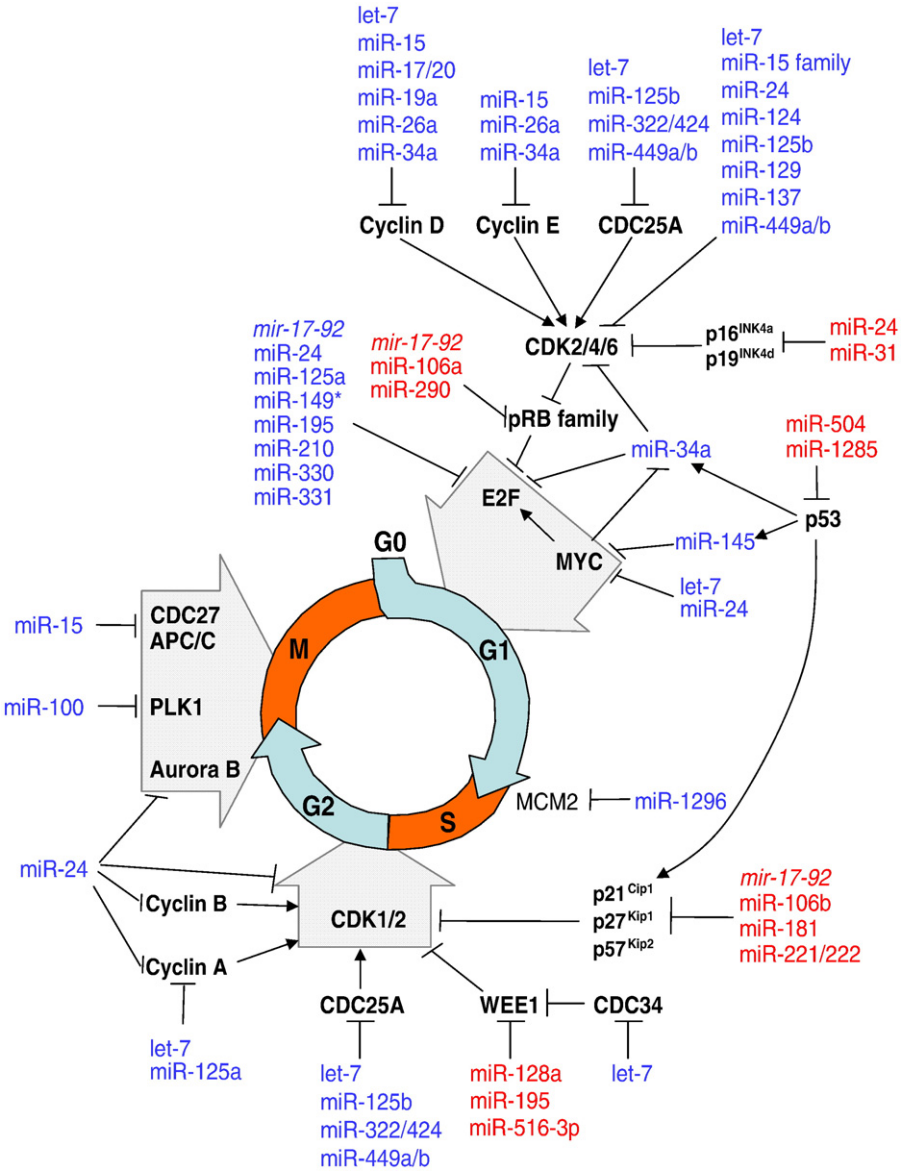

Fig. 1. An overview to cell cycle control by microRNAs. Some interactions have been omitted for clarity. let-7 (let-7a-f) and miR-15 (miR-15, miR-16 and miR-195) indicate several members of the corresponding family. Most miRNA names correspond to mature forms whereas miRNAs clusters are shown in italics. miRNAs with proliferative potential are shown in red whereas antiproliferative miRNAs are in blue. S, S-phase; M, Mitosis; G1 and G2 indicate transition phases of the cell cycle whereas G0 indicate quiescent cells. Please note that most of these interactions come from luciferase reporter assays and need to be validated using additional methods.

(such as $p16^{INK4a}$ or $p27^{Kip1}$) or pRB are a common finding in human cancer, suggesting that the proper control of the protein levels of these regulators is crucial for cell division [1]. As indicated above, the levels of cell cycle regulators may be controlled by post-transcriptional mechanisms. Among them, the central role of proteolysis in the timely elimination of cell cycle regulators is well established [6–8]. Recent evidences suggest that microRNAs (miRNAs) may also control the levels of multiple cell cycle regulators and may therefore control cell proliferation. In fact, deregulation of miRNAs may also lead to proliferative diseases such as cancer by altering the protein levels of critical oncogenes or tumor suppressor genes [9,10]. Not surprisingly, the expression of miRNAs is controlled by typical cell cycle pathways suggesting that miRNAs should also be considered as important players of the mammalian cell cycle.

2. Control of the cell cycle by miRNAs

miRNAs are a class of endogenously expressed, noncoding RNAs that control the stability and translation of protein-coding mRNAs [11,12]. These small (18–25 nucleotides) RNAs are incorporated into miRNA–protein complexes that bind the 3′ untranslated region (3′UTR) of target mRNAs [13]. These target regions display partial complementary homology with miRNAs and the binding of miRNA–protein complexes can be avoided by mutating critical target residues in the 3′UTR of target transcripts. The corresponding nucleotides in the mature miRNA sequence that display homology with the target mRNAs are known as the 'seed' sequence. The binding of miRNA–protein complexes to mRNAs may inhibit translation or destabilize target transcripts resulting in the downregulation of the protein encoded by the respective mRNA [12]. Bioinformatics estimates suggest that more than 30–60% of the human genome may be subjected to regulation by miRNAs [12,14]. By modulating the expression of target transcript, miRNAs can therefore affect many different signaling pathways and cellular processes such as proliferation, differentiation or apoptosis [15–17]. No wonder, the control of critical targets by miRNAs has multiple implications in cancer [10,18] and miRNAs can also considered as cancer targets [19,20].

2.1. Control of the G1/S transition by miRNAs

One of the first solid links between miRNAs and cell cycle regulation was established in the analysis of the anti-proliferative potential of the *mir-15a-16-1* cluster. This cluster expresses two mature miRNAs, miR-15a and miR-16, that share a similar seed sequence and therefore belong to the same miRNA family (miR-15 family). Interestingly, the *mir-15a-16-1* cluster was identified as the target of some specific chromosome aberrations in chronic lymphocytic leukemia (CLL) patients in the pioneer study that first linked genetic aberrations in miRNA with cancer [21]. This miRNA cluster is deleted and/or down-regulated in about 70% of CLL [21], as well as in pituitary adenomas [22] , prostate cancer [23,24] and in gastric cancer cell line [25], suggesting an important role in tumor development.

The *mir-15a-16-1* cluster may induce cell cycle arrest at the G1 phase by targeting critical cell cycle regulators such as CDK1, CDK2 and CDK6 as well as cyclins (D1, D3 and E1) [24,26–28]. In fact, these major cell cycle kinase complexes are regulated by several other miRNAs (Fig. 1 and Table 1). Thus, CDK4 or CDK6 mRNAs are also targeted by miR-24, miR-34a, miR-124, miR-125b, miR-129, miR-137, miR-195 (another member of the miR-15 family), miR-449 and let-7 family members [29–37]. Several positive regulators of CDK4/6 activity are also targeted by miRNAs such as D-type cyclins or CDC25A, a phosphatase that eliminates inactivating phosphates in CDKs (Fig. 1 and Table 1). D-type cyclins are major integrators of mitogenic signaling as their synthesis is one of the main endpoints of the RAS/RAF/MAPK pathway as well as other mitogenic routes [38]. The levels of D-type cyclins are downregulated by let-7, miR-15 family, miR-17, miR-19a, miR-20a, and miR-34, [23,32,35,37,39–42]. miR-26a directly downregulates cyclins D2 and E2 and induces a G1 arrest of human liver cancer cells *in vitro*. AAV-mediated miR-26a delivery potently suppresses cancer cell proliferation and activates tumor-specific apoptosis *in vivo*, resulting in dramatic suppression of tumor progression without toxicity [39]. miR-16 and miR-34a are also able to downregulate cyclin E [28]. As expected, most of these miRNAs display antiproliferative properties, function as tumor suppressors and they are inactivated in cancer by different mechanisms (Table 1). For instance, miR-124 and miR-137 are silenced by hypermethylation in tumor cells of different origins leading to CDK6 overexpression [43]. The overexpression of CDK/cyclin complexes is likely to result in increased phosphorylation of pRB thus liberating active E2F factors to drive G1 progression and S-phase entry.

The first study that revealed that E2F is targeted by miRNAs was by O'Donnell et al. [44]. These authors showed that E2F1 is negatively regulated by two miRNAs of the *mir-17-92* cluster, miR-17-5p and miR-20a [see also [45]]. Moreover, the levels of those microRNAs inversely correlate with E2F1 levels in tumors samples from colon cancer patients, suggesting that these miRNAs promote malignancy in many tissues by rendering cells insensitive to the apoptotic abilities of E2F1 [46]. In addition to the *mir-17-92* cluster, other miRNAs play a role in cell cycle progression by downregulating E2Fs. E2F1 is inhibited by miR-149*, miR-330 and miR-331-3p resulting in cell cycle arrest in prostate and gastric cancer cells [47–49]. E2F3, on the other hand, is targeted by miR-125b, miR-210 and miR-195 [35,50,51] (Fig. 1 and Table 1).

miRNAs are also able to facilitate cell cycle entry and G1 progression by targeting negative regulators of the CDK4/pRB pathway. pRB itself is targeted by miR-106a and the overexpression of this miRNA results in pRB downregulation in cancer cells [52]. Other members of the pRB family, p107/RBL1 and p130/RBL2 are controlled by two microRNA clusters, *mir-290* and *mir-17-92* [53–55]. Expression of a single miRNA of the *mir-17-92* cluster, miR-17-5p, is sufficient to drive a proliferative signal in cultured cells [55]. Downregulation of the *mir-290* cluster, on the other hand, leads to increase mRNA leves of RBL2 whose product downregulates DNA methylase expression leading a significant hypomethylation of the genome. These findings indicate that miRNAs of the miR-290 family may have important roles in fundamental processes such as epigenetic regulation in addition to development and tumorogenesis [53].

Finally, some cell cycle inhibitors of the INK4 or Cip/Kip families are also tightly regulated by miRNAs. $p16^{INK4a}$, a CDK4/6 specific inhibitor, is controlled by miR-24 and miR-31 [31,56]. Both miRNAs are involved in the regulation of cell proliferation and progress through the cell cycle at least in part by regulating the levels of this CDK inhibitor. $p21^{Cip1}$, a p53 target, is a direct target of *mir-17-92* and miR-106b [57,58]. $p27^{Kip1}$ and $p57^{Kip2}$ are controlled by miR-221/222 and miR-181 [58–60]. Ectopic expression of the *mir-221-222* cluster is thought to activate CDK2 and enhance tumor growth by negatively regulating both $p27^{Kip1}$ and $p57^{Kip2}$ [61].

2.2. Entry and progression through mitosis

Although most cell-cycle-targeting miRNAs modulate cell cycle entry and the G1/S transition, a few examples exist for the role of miRNAs in later phases of the mammalian cell cycle. Once cells have duplicated their genome, the control of the cell cycle is mostly driven by CDK1 in complex with cyclin A or cyclin B (CDK2 is also activated by A-type cyclins). miR-125b, miR-24 and let-7 miRNAs are able to downregulate the expression of Cyclin A or Cyclin B [40,51,62]. miR-195, miR-516-3p and miR-128a can also downregulate WEE1, a kinase that function as a negative regulator of the CDK1-Cyclin B complex at the G2/M transition [63,64]. As described in the previous section, the control of Cip/Kip CDK inhibitors by miRNAs may also affect mitotic entry by modulating CDK1 activity.

Not many other examples of miRNAs regulating mitosis exist. Polo-like kinase 1 (PLK1) is a critical regulator of mitosis at several levels. This kinase phosphorylates CDC25C, which in turn activates CDK1-Cyclin B1 complexes, resulting in its translocation into the nucleus and mitotic entry [65]. miR-100 has been proposed to target PLK1 mRNA, and downregulation of miR-100 leads to PLK1 overexpression in naso-pharyngeal cancer cell [66]. Finally, Aurora B kinase, a protein that functions in the attachment of the mitotic spindle to the centromeres, has been recently described as a target of miR-24 which recognizes seedless but highly complementary sequences in the Aurora B-encoding transcript [62]. Yet, the functional significance of the control of these mitotic proteins by miRNAs remains mostly unexplored.

3. Cell cycle-dependent regulation of miRNAs

miRNA-encoding genes are transcribed by RNA polymerases II or III to yield primary transcripts (pri-miRNAs), which are then processed by the nuclear RNase III Drosha to form stem-loop structures. These pre-miRNAs are transported to the cytoplasm where the RNase III Dicer cleaves the double-stranded portion of the hairpin and generates a double strand RNA that is subsequently unwound giving rise to the mature miRNA [12,67]. In general, transcription of miRNAs is thought to be regulated similarly to that of protein-coding genes.

At least 10% of the human genome is known to be regulated in a cell-cycle dependent manner [68]. The induction of miRNAs in a cell-cycle dependent manner has been recently studied in primary fibroblasts stimulated with serum suggesting a similar ratio of cell-cycle regulated miRNAs [69,70]. In fact, several miRNAs are known to be induced or repressed by critical transcription factors that control the cell cycle (Table 2).

3.1. Transcriptional regulation of miRNAs by MYC

c-MYC is a transcription factor that regulates numerous genes thus playing an important role in cellular processes such as development,

Table 1
Control of cell cycle regulators by microRNAs and relevance of these small RNAs in cancer.

miRNA	Cell cycle regulator[a]	Deregulation in cancer[b]	References
let-7 family	CDC25A, CDC34, CDK4, CDK6, Cyclin A, D1, D2 and D3, c-MYC	Downregulated in leukemias, lymphomas, melanoma, lung, breast, gastric, gastric, pancreatic, pituitary, ovarian, kidney, prostate and colon cancer, hepatocellular carcinoma, multiple myeloma.	[37,40,82,112,113, 127,128,141]
miR-15 family (miR-15, miR-16 and miR-195)	CDC27, CDK6, Cyclin D1, D3 and E1, E2F3 and WEE1	Downregulated in CLL, DLBCL, multiple myeloma, pituitary adenoma, prostate and pancreatic cancer	[23,26–28,35, 63,64,69]
mir-17-92 cluster (miR17, miR-18a, miR-19a; miR-20a; miR-19b-1; miR-92-1) and paralogous clusters (mir-106a-92-2 and mir-106b-25)			
miR-17 family (miR17, 20, 106, 93)	Cyclin D1, E2F1, MYCN, p21Cip1 and pRb family	Overexpression in lung and colon cancer, lymphoma, multiple myeloma, medulloblastoma. Downregulated in melanoma, ovarian and breast cancer	[41,44,45,54,55,57, 58,79,93,117,119]
miR-19a	CyclinD1	Deregulated in leukemias, hepatocellular carcinoma, colorectal and lung cancer	[42]
miR-25	p57Kip2	Deregulated in glioblastoma, hepatocellular carcinoma, colorectar, gastric, pancreatic and prostate cancer	[58]
miR-24	AURKB, CDK1, CDK4, Cyclin A2, Cyclin B, E2F2, MYC, $p16^{INK4a}$	Deregulated in some leukemias, hepatocellular carcinoma and prostate cancer	[31,62]
miR-26a	Cyclin D2 and E2	Downregulated in leukemia, Burkitt lymphomas, glioma, pituitary, thyroid, liver, kidney, ovarian, bladder and breast cancer	[39]
miR-31	$p16^{INK4a}$, $p19^{INK4d}$	Deregulated in bladder, breast, colorectal, liver, lung, pancreatic and prostate cancer	[56]
miR-34a	CDK4, CDK6, Cyclin D1, Cyclin E2, E2F1, E2F3 and c-MYC	Deregulated in CLL, medulloblastoma, neuroblastoma, retinoblastoma, glioblastoma, colorectal, liver, melanoma, pancreatic, thyroid and prostate cancer	[32,98,104]
miR-100	PLK1	Deregulated in bladder, ovarian, pancreatic, prostate and nasopharyngeal cancer	[66]
miR-124a	CDK6	Deregulated in ALL, CLL, medulloblastoma, hepatocellular carcinoma and breast, colorectal and lung cancer	[29,30,142]
miR-125b	CDC25A, CDK6, Cyclin A, E2F3	Deregulated in neuroblastoma, medulloblastoma, liver, bladder, breast and prostate cancer	[33,51]
miR-128a	WEE1	Deregulated in ALL, AML, glioblastoma, pituitary adenomas and breast cancer	[63,64]
miR-129	CDK6	Reduced expression in multiple tumor cell lines and primary tumors (medulloblastoma, undifferentiated gastric cancers, lung adenocarcinoma, endometrial, ovarian and bladder cancer and colorectal and hepatocellular carcinoma)	[118]
miR-137	CDK6	Deregulated in colorectal cancer and hepatocellular carcinoma	[29,30,142]
miR-145	c-MYC	Deregulated in leukemias, Burkitt lymphomas, bladder, breast, colorectal, ovarian, gastric, lung, pancreatic, prostate cancer and hepatocellular carcinoma	[143]
miR-149*	E2F1	Neuroblastoma	[47]
miR-155	WEE1	Deregulated in leukemias and lymphomas, Pituitary Adenomas, hepatocellular carcinoma, breast, colorectal, ovarian, lung and pancreatic cancer	[63,64]
miR-181 family (miR-181a, b and c)	p27Kip1	Deregulated in leukemias, glioblastoma, hepatocellular carcinoma, breast, colorectal, lung, pancreatic and prostate cancer	[60]
miR-210	E2F3	Deregulated in leukemias, lymphomas, glioblastoma, breast, kidney, lung, pancreatic, prostate and ovarian cancer	[50]
miR-221 family (miR-221 and miR-222)	$p27^{Kip1}$, $p57^{Kip2}$	Deregulated in leukemias, glioblastoma, breast, pancreatic, prostate, ovarian, bladder, and gastric cancer, melanoma and hepatocellular carcinoma	[58,59,121,122, 144,145]
miR-290 cluster	p130/RBL2		[53]
miR-330	E2F1	Downregulated in follicular lymphoma, oral squamous cell carcinoma and prostate cancer	[48]
miR-331-3p	E2F1	Human gastric cancer	[49]
miR-322/424, miR-503	CDC25A	Deregulated in some leukemias, kidney, ovarian and pancreatic cancer.	[146]
miR-449a/449b	CDC25A, CDK6	Downregulated in prostate cancer	[95]
miR-503	CDC25A	Deregulated in retinoblastoma and prostate cancer	[146]
miR-504	p53		[147]
miR-516a-3p	WEE1	Upregulated in breast cancer and in pituitary adenomas	[63,64]
miR-1285	p53		[148]
miR-1296	MCM2	prostate cancer	[149]

[a] Note that most of these interactions have been only validated using luciferase reporter assays.
[b] Data from the indicated references or from http://www.mir2disease.org/.

differentiation, cell proliferation and apoptosis [71–73]. c-MYC also controls the cell cycle by modulating the levels of several regulators of progression through G1 as well as DNA replication. Deregulated expression of c-MYC has been detected in a wide variety of human cancers, including breast and colon, and is often associated with aggressive, poorly differentiated tumors [74,75]. c-MYC also controls the production of many non-coding RNAs, including tRNA, rRNA and miRNAs, and these RNAs are likely to contribute substantially to the complex biology and pathology that is associated with c-MYC [76,77].

In a pionner study in 2005, J.T. Mendell and coworkers reported the direct induction of the *mir-17-92* cluster by c-MYC [44]. This cluster of six miRNAs is considered as an oncogene and cooperates with c-MYC to accelerate tumor development in a mouse model of B-cell lymphoma [78]. Expression of *mir-17-92* is high in proliferating cells and this miRNA cluster has also been functionally implicated in several solid tumors as well as in tumor angiogenesis [52,79]. This cluster, as well as the paralogous cluster *mir-106a-92-2*, are also induced by MYCN, a transcription factor shown to promote cell cycle progression in neuroblastoma cells [80]. Other miRNAs were also induced after overexpression of MYCN in the same study although direct binding to target promoters was not tested. Both c-MYC and MYCN also induce miR-9, a miRNA that targets *CDH1*, the E-cadherin-encoding mRNA, leading to increased cell motility and invasiveness, as well as to increased tumor angiogenesis [81].

Despite the relevance of the induction of the *mir-17-92* cluster and miR-9 by c-MYC, the activity of this transcription factor has a major effect as a repressor of many other miRNAs. miRNA expression has been reported to be globally reduced in tumor samples and inhibition of miRNA biogenesis accelerates tumorigenesis in vivo [82]. c-MYC may participate in the tumor-associated repression of miRNAs by directly repressing several miRNA clusters such as *mir-15a-16-1*, miR-22, miR-23a/b, miR-26, miR-29 and several let-7 clusters [83]. Many of

Table 2
Cell cycle-dependent regulation of miRNA expression by transcription factors.

Cell cycle regulator	miRNA gene or cluster	Relationship	References
c-MYC	*let-7* (several clusters)	Repression	[83]
	mir-9	Induction	[81]
	mir-15a-16-1	Repression	[83]
	mir-17-92	Induction	[44]
	mir-22	Repression	[83]
	mir-23a-24-2 and *mir-23b-24-1*	Repression	[150]
	mir-26a-1 and *mir-26a-2*	Repression	[83]
	mir-26b	Repression	[83]
	mir-29b-2-29c and *mir-29b1-29a*	Repression	[83]
	mir-30e-30c-1	Repression	[83]
	mir-34a	Repression	[83]
	mir-146a	Repression	[83]
	mir-150	Repression	[83]
	mir-497-195	Repression	[83]
MYCN	*mir-9*	Induction	[81]
	mir-17-92	Induction	[80]
	mir-106a-92-2	Induction	[80]
	mir-221-222	Induction	[80]
E2Fs (mostly E2F1 and E2F3)	*let7a-d*	Induction	[69]
	let7i	Induction	[69]
	mir-15b-16-2	Induction	[69]
	mir-17-92	Induction	[44,91]
	mir-106b-25	Induction	[69]
	mir-449c-b-a	Induction	[95]
p53	*mir-34a* and *mir-34b-/c*	Induction	[98,100–104]
	mir-143-145	Induction	[106]
	mir-194-2-192	Induction	[105]
	mir-194-1-215	Induction	[105]

these miRNAs downregulated by c-MYC are known tumor suppressors and target critical cell cycle regulators (Fig. 1 and Table 1). For instance, the *mir-15a-16-1* locus is deleted or downregulated in over two-thirds of individuals with chronic lymphocytic leukemia [21,84]. On the other hand, the mature miR-15a and miR-16 miRNAs target several cell cycle genes (Table 1) although since most of these targets have been validated in other cell types it is not clear two what extent the anti-tumoral effect of these miRNAs relies in their cell cycle effect. Several of the other c-MYC-repressed miRNAs also have marked anti-tumorigenic activity in a mouse model of B cell lymphoma [83].

Although most of these miRNAs are downregulated through the transcriptional repressor activity of c-MYC, this protein may also lead to miRNA downregulation by alternative mechanisms. Thus, c-MYC is able to block the maturation of specific miRNAs by inducing the RNA binding proteins Lin28 and Lin28b [85,86], which are known to act as negative regulators of let-7 maturation at multiple levels including Drosha and Dicer processing [77]. Repression of multiple miRNAs by c-MYC is likely to be an important mechanism contributing to the reduced function of miRNAs in cancer cells [77].

3.2. E2F-dependent transcription of miRNAs

The E2F family of transcription factors plays a central role in the control of cell cycle progression by regulating the timely expression of genes required for DNA synthesis and mitosis at the G1/S phase boundary [87–89]. Global gene expression profiling and promoter occupancy studies have confirmed that many proteins crucial for cell cycle progression are E2F targets [90]. Recent studies have also reported direct regulation of several miRNAs by E2F transcription factors. E2F1-3 directly bind the promoter of the *mir-17-92* cluster, a cluster that displays both oncogenic and tumor suppressor activities, inducing its transcription [91,92]. Since several *mir-17-92* miRNAs, such as miR-17-5p and miR-20a, are able to repress E2F factors [44], these results suggest an autoregulatory feedback loop that may be important for preventing an abnormal accumulation of E2F1-3 and proper regulation of cellular proliferation and apoptosis [91,92]. The *mir-106b-25* cluster is also activated by E2F1 in parallel with its host gene, *MCM7*. In turn, miR-106b and miR-93 also regulate E2F1 expression, establishing a second miRNA-directed negative feedback loop [93,94]. E2F1 induces the *mir-106b-25* cluster leading to their accumulation in gastric primary tumors [93]. The *mir-449c-b-a* cluster is also a direct transcriptional target of E2F1. These miRNAs are expressed from the first intron of the *CDC20B* gene and share a common promoter with the host gene. miR-449a/b target and inhibit oncogenic CDK6 and CDC25A resulting in pRB dephosphorylation and cell cycle arrest at G1 phase, revealing a new negative feedback regulation of the pRB-E2F1 pathway. miR-449a/b expression is epigenetically repressed in cancer cells, suggesting a tumor suppressor function of miR-449a/b [95].

The overall induction of miRNAs by E2F transcription factors has been recently analyzed using expression profiles and chromatin immunoprecipitation assays. At least four miRNA clusters, *let-7a-d*, *let-7i*, *mir-15b-16-2*, and *mir-106b-25*, are direct targets of E2F1 and E2F3 during G1/S and are repressed in E2F1/3 null cells [69]. Interestingly, these miRNAs do not contribute to E2F-dependent entry into S phase but rather inhibit the G1/S transition by targeting multiple cell cycle regulators and E2F targets. In the absence of these miRNAs, E2F induces a stronger DNA replication activity that results in replicative stress and the corresponding DNA damage response (Fig. 2). Thus, E2F-induced miRNAs contribute to limiting the cellular responses to E2F activation, thus preventing replicative stress [69]. Additional miRNAs are also induced by E2F factors during cell cycle entry although the consequences of this regulation have not been studied in detail [69]. Given the known function of E2F in inducing other oncogenic miRNAs such as the *mir-17-92* and *mir-221-222* clusters (Fig. 2), control of miRNAs by E2F is likely to play multiple roles in cell proliferation and in proliferative diseases such as cancer.

3.3. Stress-mediated induction of miRNAs

The tumor suppressor p53 acts as a transcription factor that regulates the expression of numerous genes, leading to cell cycle arrest, apoptosis, and senescence in response to a variety of stress signals [96]. Among these functions, p53 mediates the cell cycle arrest in response to DNA damage by transcriptional induction of the CDK inhibitor $p21^{Cip1}$.

Several groups reported in 2007 the induction of the miR-34 family (miR34a, b and c) by p53 in response to stress signals [97–104]. p53 directly binds to the promoter of the *mir-34a* transcript and the *mir-34b-34c* cluster, inducing their expression at the transcriptional level. Ectopic expression of the miR-34 family induces cell cycle arrest and apoptosis by down-regulating Cyclin D1, Cyclin E2, E2F transcription factors as well as CDK4 and CDK6 among other proteins [32,98,103] (Fig. 1 and Table 1). miR-34a is therefore thought to contribute to a $p21^{Cip1}$-independent mechanisms through which p53 induces G1 arrest [99].

Two additional clusters of miRNAs, *mir-194-2-192* and *mir-194-1-215*, are induced by p53, leading to the up-regulation of miR-192, miR-194, and miR-215 [105]. These miRNAs were detected at high levels in normal colon tissue but were severely reduced in many colon cancer samples. On the other hand, miR-192 and its cousin miR-215 can each contribute to p53 activity and $p21^{Cip1}$ levels. These effects were partially dependent on the presence of wild-type p53, suggesting that they function as an internal amplifier of $p21^{Cip1}$ induction by p53 (Fig. 3). miR-192 and miR-215 are capable of inducing cell cycle arrest, but they trigger cell death only with lower efficiency than miR-34a [105]. It has been also reported that p53 directly induces miR-145, a miRNA that subsequently represses c-MYC, thus linking p53 with the downregulation of c-MYC-dependent oncogenic pathways [106] (Fig. 3). In general, the induction of miRNAs represents an attractive

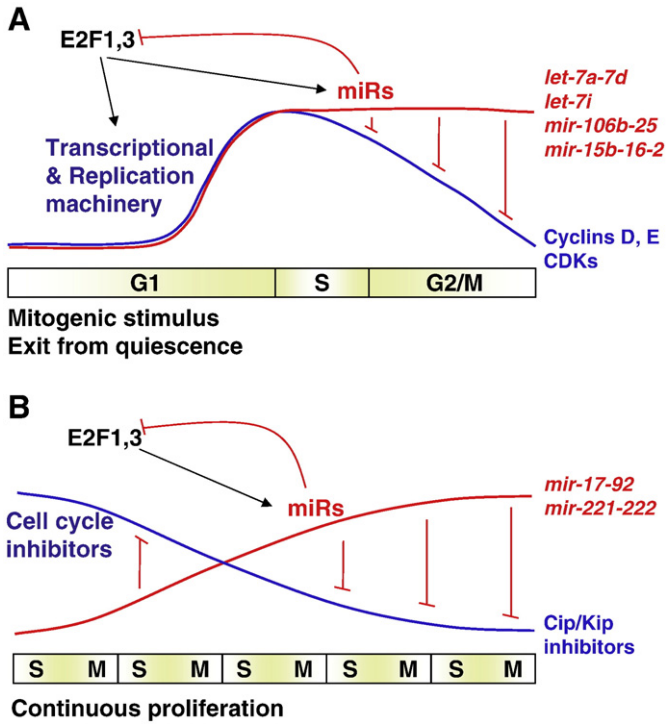

Fig. 2. A model for the role of miRNAs induced by E2F transcription factors during the cell cycle. A, Upon mitogenic signaling and during cell cycle entry, E2F factors become active and induce the transcription of their target protein-coding genes (e.g. Cyclin E) as well as specific miRNA clusters (*let-7a-7d*, *let-7i*, *mir-15b-16-2* and *mir-106b-25*). Whereas proteins induced by E2F trigger DNA replication, E2F-induced miRNAs maintain low levels of cell cycle regulators and E2F targets (e.g. Cyclin E) to limit the effect of E2F factors and possible to avoid replicative stress. B, In continuously growing cells, other miRNA clusters such as *mir-17-92* and *mir-221-222* accumulate and may participate in maintaining low levels of cell cycle inhibitors such as members of the Cip/Kip family of CDK inhibitors thus promoting stable proliferation.

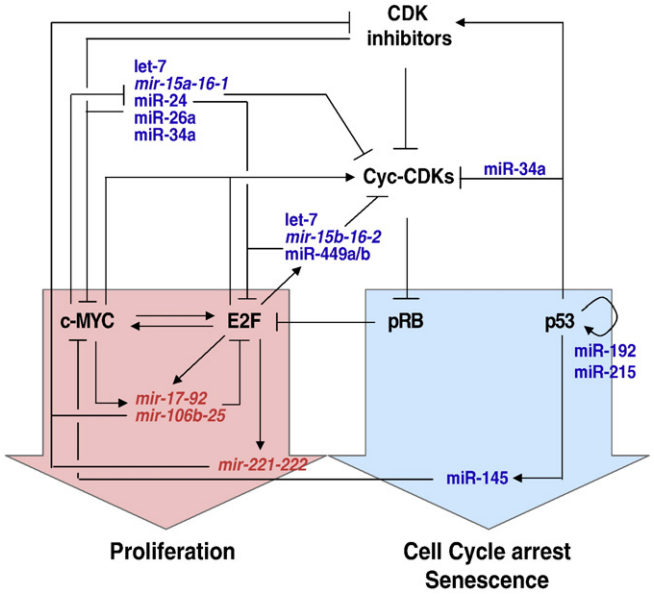

Fig. 3. Networks between miRNAs and transcriptional regulators of the cell cycle. Only a few miRNAs are indicated and additional connections between the indicated regulators have been omitted for clarity.

mechanism for the downregulation of several cell cycle or oncogenic proteins observed after p53 activation.

Finally, several miRNAs are repressed by p53 in a E2F-dependent manner [107]. These miRNAs include the three *mir-17-92* paralogous clusters (*mir-17-92-1*, *mir-106a-92-2* and *mir-106b-25*) as well as *mir-15b-16-2* and *mir-155* [107]. Several of these miRNAs are induced by E2F1 and E2F3 transcription factors and regulate multiple E2F-target coding genes [69,107]. Interestingly, the levels of these miRNAs do not significantly change upon DNA damage suggesting a specific link to the antiproliferative signals induced during senescence.

4. A complex network of interactions between miRNAs and transcriptional factors

As suggested by the experimental data described in the previous sections, miRNAs and transcriptional regulators cooperate in multi-gene transcriptional and post-transcriptional feed-forward (Fig. 3). p53 can suppress c-MYC at the transcriptional level and the p53 downstream gene, $p21^{Cip1}$, is able to cause c-MYC repression. On the other hand, p53 downregulates c-MYC through miR-145 [106]. p53 also represses several miRNAs in a E2F-dependent manner [106,107]. How p53 represses E2F factors is not clear at this moment although it may be mediated by the $p21^{Cip1}$- or miR-34a-mediated inhibition of Cyclin-CDK complexes (Fig. 3).

E2F and c-MYC transcriptional factors also display multiple connections. E2F1 and c-MYC positively regulate each other and expression of E2F1 is negatively regulated by two miRNAs, miR-17-5p and miR-20a, expressed from the *mir-17-92* cluster induced by c-MYC [44] (Fig. 3). Thus, the repression of E2F by these c-MYC-induced miRNAs may provide fine-tuning regulation to control the opposing proliferative and apoptotic functions of E2F. miR-24, which is repressed by c-MYC [83], is also able to inhibits cell proliferation by targeting E2F and c-MYC transcription factors, as well as other cell cycle regulators [62].

The control of miRNAs by E2F transcriptional factors involves many different interactions that are difficult to understand simply as proliferative versus antiproliferative functions. On one hand, E2F (as well as c-MYC) activates the cell cycle proliferation program by inducing critical cell cycle genes such as cyclins or CDKs. Moreover, E2F induce the oncogenic *mir-17-92*, *mir-106b-25* and *mir-221-222* clusters leading to the downregulation of all members of the Cip/Kip family of CDK inhibitors (Fig. 3). On the other hand, some of the miRNAs expressed in these clusters downregulate E2F factors themselves. In addition, E2F induce antiproliferative miRNAs expressed by *let-7*, *mir-15b-16-2* or *mir-449-c-b-a* clusters, which also downregulate E2F factors as well as many other positive regulators of the cell cycle. It is now well established that the excess of proliferative signals may provoke replicate stress and that the checkpoints that respond to this stress act as an antiproliferative barrier in cancer [108]. Thus, it is tempting to speculate that the regulatory loops provide by miRNAs may help preventing replicative stress induced by proliferative signals [69]. The downregulation of several of the miRNAs involved in these regulatory loops, such as members of the let-7 or miR-15 families, could therefore explain the replicative stress observed in the early phases of tumor development.

5. Relevance in human disease/cancer

The relevance of miRNAs to cancer was suggested by changes in their expression patterns [52,109] and recurrent amplification and deletion of miRNA genes in tumors [21,110]. This has been translated in several cases into functional validation of roles in tumor initiation and progression using mouse models and cultured tumor cells. Several miRNAs have emerged as candidate components of oncogene and tumor-suppressor networks. The *mir-17-92* cluster [44,78], and miR-155/BIC [111] have been implicated as proto-oncogenes in B-cell lymphomas. On the other hand, the *mir-15a-16-1* cluster is frequently

deleted in patients with chronic lymphocytic leukaemia (CLL) [21], and evidence from expression studies and functional studies revealed the potential tumor-suppressive roles of let-7 in various cancers [112,113], possibly owing to its ability to repress key oncogenic components, including RAS and HMGA2. Several other miRNAs have been classified as oncogenic or tumor-suppressive genes according to their function in cellular transformation and expression in tumors [9,10,18,114].

Many of the oncogenic or tumor-suppressor miRNAs target cell cycle regulators (Table 1) and this interaction may at least partially explain the oncogenic function of the miRNA alteration in cancer cells. The major oncogenic or tumor-suppressor miRNAs are good examples of the relevance of targeting the cell cycle for their tumor-related functions. The first oncogenic miRNA gene, *mir-17-92*, downregulates $p21^{Cip1}$ and pRB family members [57,58,115–119] and *mir-221-222* exerts it oncogenic function through the downregulation of $p27^{Kip1}$ and $p57^{Kip2}$, leading to the activation of Cyclin-CDK complexes and cell cycle progression [61,120–122]. On the other hand, major tumor-suppressor miRNAs, such as the members of the let-7 or miR-15 families, downregulate a wide spectrum of positive regulators of the cell cycle. The cancer growth-suppressive activity of let-7 miRNAs has since been validated in many human tumors, including colon, lung and breast cancer [123–126]. In addition to members of the RAS family, these miRNAs target the cell-cycle regulators CDK4, CDK6, CDC25A, cyclin D1, D2 and D3, cyclin A or CDC34 as demonstrated by different techniques [37,82,112,113,127,128]. The miR-15 family members, miR-15 miR-16 and miR-195, are bona-fide tumor suppressors and are also master regulators of the cell cycle by targeting critical regulators such as CDC27, CDK6, Cyclin D1, D3 and E1 or E2F3 factors [23,26,27,129–132]. The involvement of other cell-cycle targeting miRNAs in human cancer is summarized in Table 1.

6. Conclusions and perspectives

It is now obvious that miRNAs are functionally integrated into many crucial cell-cycle control pathways. Many miRNAs are anti-proliferative and this function may be mediated by the control of different mitogenic pathways including the routes that lead to activation of CDKs. A few miRNAs induce proliferation in many cases by targeting CDK inhibitors or members of the pRB family (Fig. 1). This classification is not as simple as some miRNAs, such as the ones expressed in the *mir-17-92* cluster, may target both positive and negative regulators of the cell cycle (Table 1). In addition, the control of miRNAs by cell-cycle-dependent transcription factors adds a new level of complexity. For instance, transcription factors that positively regulate cell cycle progression, such as c-MYC or E2F family members, may induce antiproliferative miRNAs to control the extent of mitogenic signaling and prevent replicative stress (Figs. 2 and 3).

Despite all the knowledge accumulated in the last years, we are just starting to sense the relevance of miRNAs in cell cycle control and cell proliferation. Most data summarized in this review comes from studies with reporter assays, in which the 3′-UTR of one or a few candidate mRNAs has been placed downstream of the luciferase gene and this construct is tested after over-expression of wild-type or mutated forms of the candidate miRNA. Thus, extensive efforts to develop and improve experimental techniques to show direct target regulation by miRNAs need to be made. New protocols now exist for target validation using antisense inhibition of endogenous miRNA expression using 2-O-Met technology [133], target protectors [134] or targeted delivery of antisense inhibitor miRNAs [135]. In addition, most miRNA targets are still unknown due to the lack of reliable massive techniques suggesting that we are missing a big portion of the connections between miRNAs and the cell cycle. Recent papers show how proteomics technology is a suitable approach to explore the full impact of miRNAs on protein output and to globally identify their target genes [136,137]. Finally, it is also important to discuss miRNA–target interactions in a cellular context, as associations of miRNAs and their targets determined in one cell type may not predict their association in another cell type. For instance, *miR-15a-16* is down-regulated in prostate cancer, and shares a reciprocal relation with its targets BCL2, CCND1 and WNT3A in these tumors [23]. However, the relevant targets of these miRNAs may be different and cannot be directly taken from studies in other cells types.

In addition, our understanding of regulation of miRNA biogenesis or function is very limited. For instance, recent data suggest that cell–cell contact in quiescent cells globally activates miRNA biogenesis through enhanced processing of miRNAs by Drosha and more efficient formation of RNA-induced silencing complexes [138]. How the miRNA machinery is regulated in a cell-cycle dependent manner is a relevant question that remains to be analyzed in detail. Some other results on the control of the miRNA turnover during the cell cycle or the possibility of a miRNA-dependent activation of translation have opened new perspectives in the last few years. miR-29b is degraded in all cell-cycle phases except mitosis while the levels of miR-29a, which is expressed from the same cluster, are constant [139]. These data suggest that the stability of miRNAs may be regulated in a cell-cycle-dependent manner. In addition, miRNAs might have the potential to up- or down-regulate translation depending on the cell-cycle stage of the cells. Some miRNAs such as miR-369-3 or let-7 family members may activate translation in quiescent cells while they repress translation in cycling/proliferating cells [140].

Given the relevance of cell-cycle control in tissue homeostasis and proliferative diseases, the modulation of cell cycle entry or progression by miRNAs, and the possible control of miRNA function in a cell-cycle dependent manner will be the focus of intense research in the upcoming years. The possible use of miRNAs in therapy [19,20,39] further highlights the relevance of understanding the connections between miRNAs and the cell division cycle.

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