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REVIEW

The p53/microRNA connection in gastrointestinal cancer

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Abstract: The protein encoded by the *TP53* gene is one of the most important suppressors of tumor formation, which is also frequently inactivated in gastrointestinal cancer. MicroRNAs (miRNAs) are small noncoding RNAs that inhibit translation and/or promote degradation of their target messenger RNAs. In recent years, several miRNAs have been identified as mediators and regulators of p53's tumor suppressing functions. p53 induces expression and/or maturation of several miRNAs, which leads to the repression of critical effector proteins. Furthermore, certain miRNAs regulate the expression and activity of p53 through direct repression of p53 or its regulators. Experimental findings indicate that miRNAs are important components of the p53 network. In addition, the frequent genetic and epigenetic alterations of p53-regulated miRNAs in tumors indicate that they play an important role in cancer initiation and/or progression. Therefore, p53-regulated miRNAs may represent attractive diagnostic and/or prognostic biomarkers. Moreover, restoration of p53-induced miRNAs results in suppression of tumor growth and metastasis in mouse models of cancer. Thus, miRNA-based therapeutics may represent a feasible strategy for future cancer treatment. Here we summarize the current published state-of-the-art on the role of the p53-miRNA connection in gastrointestinal cancer.
Keywords: p53, microRNA, cancer, gastrointestinal tract

Introduction

Gastrointestinal (GI) cancers represent malignant tumors of the GI tract and accessory organs of digestion. They include carcinomas arising in the oral cavity, esophagus, stomach, liver, gallbladder, pancreas, small intestine, large intestine, rectum, and anus. GI cancer represents about 30% of all tumor incidences and is responsible for approximately 40% of tumor-related mortality worldwide (Figure 1A and B).[1] Tumors of the GI tract harbor mutations in the *p53* tumor suppressor gene *(TP53)* with a prevalence ranging from 31% to 45% (Figure 1C).[2] The p53 protein functions as a transcription factor that mediates the response to many cellular stresses, most prominently the DNA damage response. p53 suppresses a variety of malignant processes, thereby representing one of the most important cancer suppressing proteins.[3] p53 protects against cancer by inducing cellular processes such as apoptosis or cell cycle arrest, thereby preventing the propagation of damaged cells that potentially could give rise to tumors.[4,5] Moreover, p53 inhibits epithelial to mesenchymal transition (EMT), stemness, and metabolic adaptations, which are typically found in tumors.[6] In addition, p53 promotes DNA repair, antioxidant defense, and differentiation. On the molecular level, p53 exerts its tumor suppressive functions by regulating the expression of numerous target genes, mainly by direct binding to specific DNA motifs located in target

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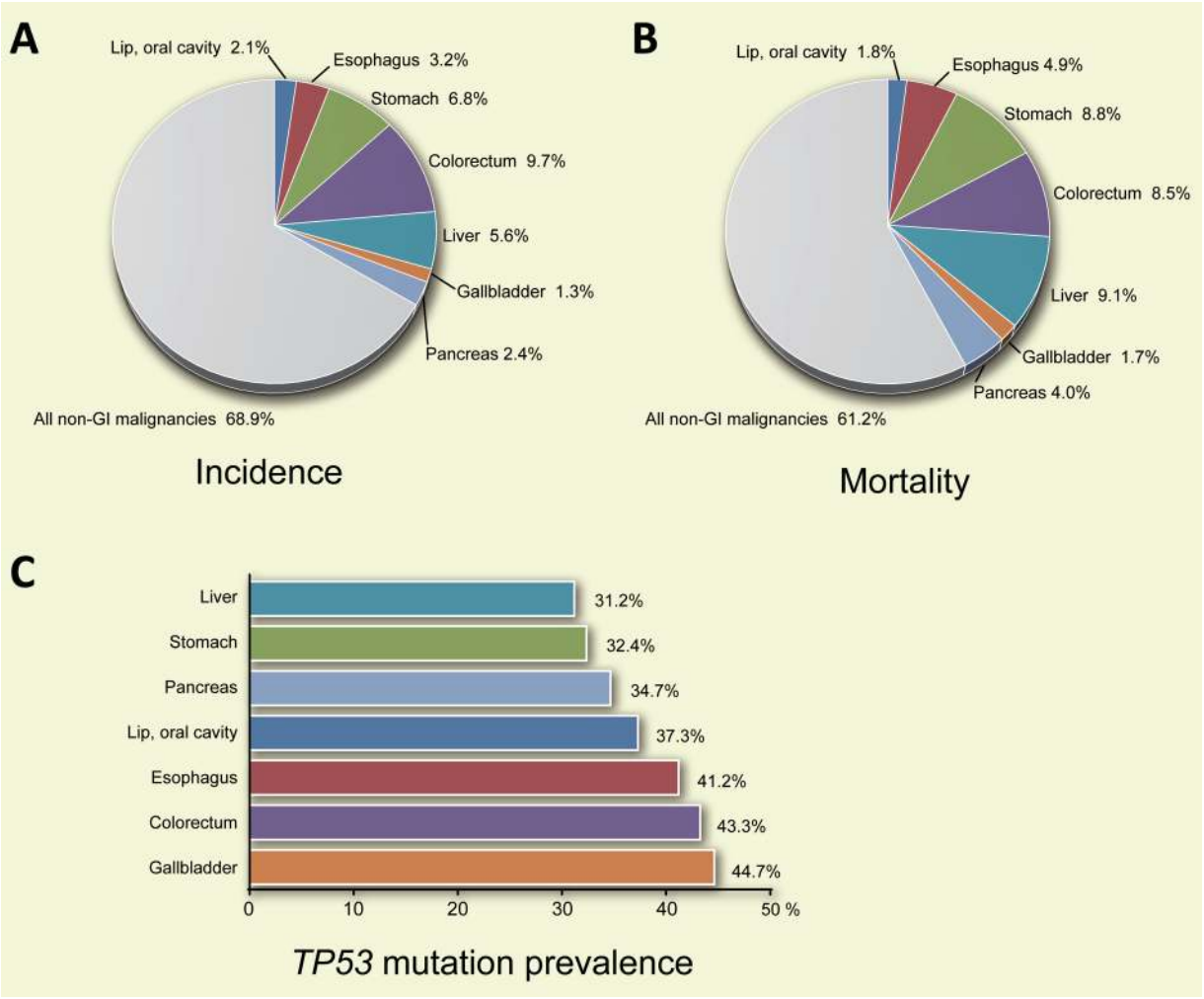

Figure 1 Incidence (**A**) and mortality (**B**) of indicated gastrointestinal (GI) cancers worldwide. (**C**) Prevalence of mutations in the *TP53* gene in the indicated GI cancers.

gene promoters.[7] Besides p53-regulated protein expression, p53-induced microRNAs (miRNAs) have emerged as important effectors of p53.[8,9] The generation of mature miRNAs is a multistage process (see Figure 2) starting with the transcription of miRNA encoding genes to yield the primary miRNA (pri-miRNA).[10] Next, the pri-miRNA is cleaved by the RNAse III enzyme Drosha, resulting in a ~70 nucleotide stem-loop-structured miRNA precursor molecule (pre-miRNA).[11] The pre-miRNA is transported to the cytoplasm by Exportin 5, where it is cleaved further by the RNAse Dicer. The resulting 20 to 25 bp mature miRNA is incorporated into the miRNA-induced silencing complex (miRISC), which mediates miRNA-induced silencing of target messenger RNAs (mRNAs).[12] miRNAs bind to 3′-untranslated regions (3′-UTR) of mRNAs via their seed sequences, which are conserved seven nucleotide regions in their 5′ region. The association of the miRISC with seed-matching sequences in target mRNAs results in the inhibition of translation and degradation of the target mRNAs.[10] It has been estimated that >60% of human protein coding genes are subject to regulation by miRNAs.[13] Not surprisingly, miRNA-mediated regulation has been implicated in almost all physiological and pathophysiological processes.[10] Interestingly, several miRNAs may also be of use for diagnostic, prognostic, and therapeutic applications in GI-cancers.[14–18] Extracellular miRNAs have been detected in blood serum. These miRNAs are either secreted by living cells via exosomes or microvesicles, or they originate from dying cells.[19] Interestingly, these circulating miRNAs are extremely stable, both in blood and after isolation. Numerous studies have shown their potential usefulness as noninvasive diagnostic and prognostic markers in GI cancers.[20] Seven years ago it was shown that p53 also regulates the expression of miRNA-encoding genes.[8] The p53-regulated miRNAs have been implicated

in the control of various cancer-related processes, such as proliferation, apoptosis, EMT, migration, invasion, and metastasis. Therefore, they may represent important mediators of the tumor suppressive function of p53. In addition, a number of miRNAs can regulate expression and activity of the p53 protein, either negatively through direct repression of p53 expression, or positively through the repression of negative regulators of p53. In this review we summarize the current knowledge about the p53/miRNA network and its role in GI cancers.

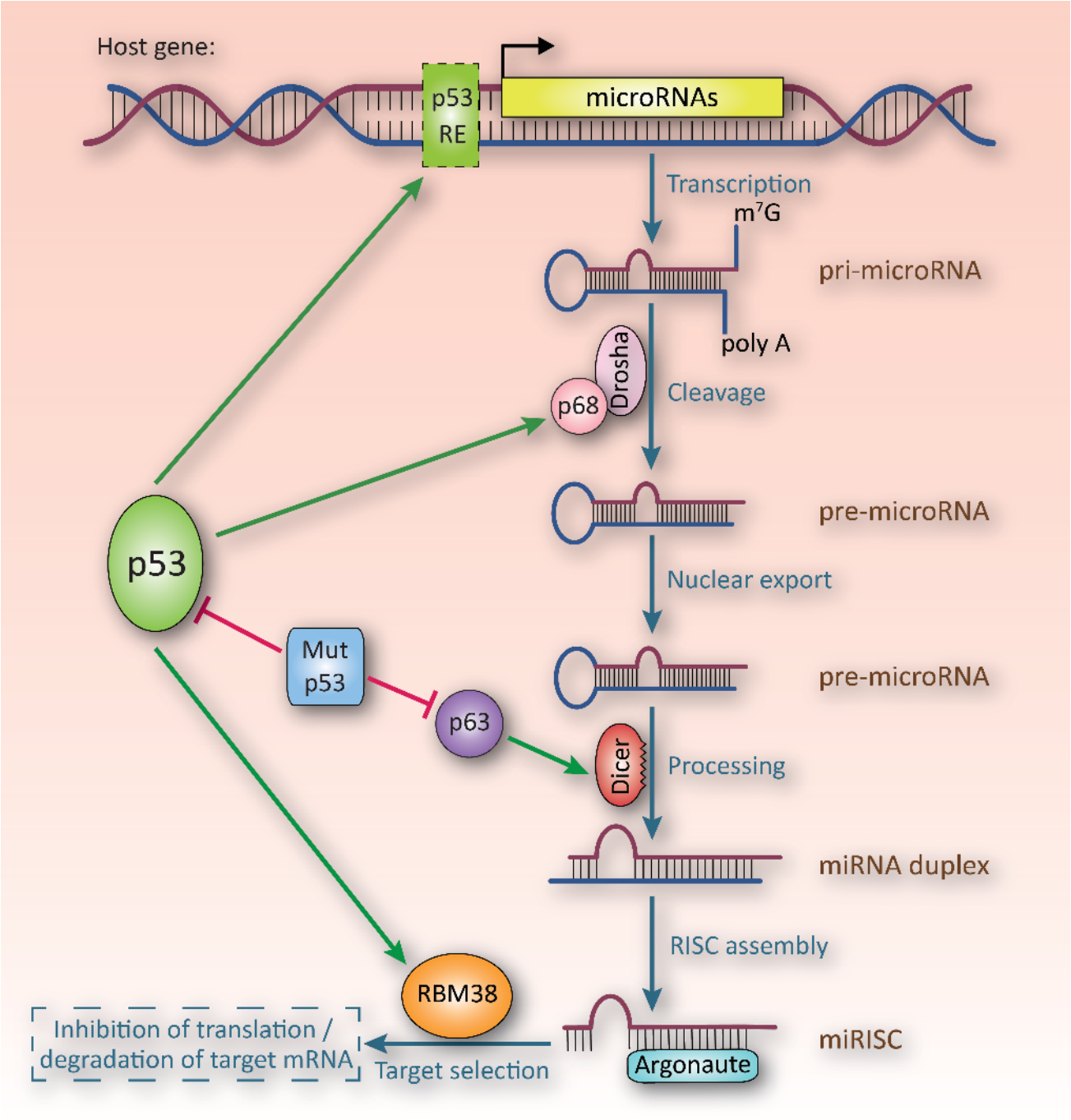

Figure 2 Effects of p53 on miRNA biogenesis.
Notes: Wild-type p53 (green) regulates miRNA transcription, processing, and target selection. In contrast, mutant p53 (blue) is unable to induce the expression of miRNAs and additionally inhibits the p63-mediated activation of the miRNA processing protein Dicer.
Abbreviations: mRNA, messenger RNA; miRNA, microRNA; pre-microRNA, miRNA precursor molecule; pri-microRNA, primary miRNA; miRISC, miRNA-induced silencing complex; mut, mutant; RE, response element.

p53 regulated miRNAs

In 2007, we and other groups identified several miRNAs as direct transcriptional targets of p53.[21–27] Since then, many of these miRNAs have been validated as important mediators of p53 functions (Table 1 and 2).[9] p53 regulates the expression of its target miRNAs either on the transcriptional level by direct binding to the promoters of the corresponding genes, or by regulating miRNA processing (Figure 2). It was shown that p53 interacts with the DEAD-box RNA helicase p68 (also known as DDX5) and enhances its interaction with the Drosha complex. As a result, p53 promotes the processing of specific pri-miRNAs to pre-miRNAs, leading to elevated levels of the respective miRNAs.[28] Another link between p53 and miRNA-processing has been observed in conditional *Dicer* knockout mice.[29] *Dicer* deficiency, and therefore incomplete miRNA maturation, induces p53, which leads to

Table 1 Summary of changes in expression of p53-pathway-related miRNAs in GI cancers

			Tumor entity				
		miRNA	CRC	EC	GC	HCC	PaC
p53- regulated miRNAs	Induced by p53	miR-34a	▼	▼	▼	▼	▼
		miR-34b/c	▼	▼/Δ	▼	▼	▼
		miR-15a/16-1	▼	Δ			
		miR-200c/141	▼/Δ	Δ	▼	▼	
		miR-200a/b/429	▼	Δ	▼		Δ
		miR-107	Δ	▼	Δ		▼
		miR-145	▼	▼	▼	▼	▼
		miR-192/194/215	▼/Δ		▼/Δ		
		miR-29	Δ		▼	▼	
		miR-605					
		miR-149	▼		▼		
		miR-22	▼	Δ	▼	▼	Δ
		miR-23b	▼	▼		▼	
		miR-205		▼		▼	
		miR-1246	▼/Δ	Δ			
		miR-1204					
	Repressed by p53	miR-17-92	Δ	Δ	Δ	Δ	Δ
		miR-224	▼/Δ			Δ	
		miR-502	▼				
miRNAs that directly target p53		miR-25	Δ	Δ	Δ		
		miR-30d	Δ			Δ	Δ
		miR-33					
		miR-98		▼			
		miR-125a		▼	▼	▼	
		miR-125b	Δ	▼	▼/Δ	▼/Δ	Δ
		miR-150	▼	▼	Δ		▼
		miR-214	Δ	▼/Δ	Δ	▼	Δ
		miR-375		▼			▼
		miR-380					
		miR-504					
		miR-1285					

Notes: For a more detailed description of the single miRNAs and references see Tables 2 and 3. Green box with ▼: downregulated in indicated GI tumor type; Red box with Δ: upregulated in indicated GI tumor type; Yellow box with ▼/Δ: down- or upregulated in indicated GI tumors.
Abbreviations: CRC, colorectal cancer; EC, esophageal cancer; GC, gastric cancer; GI, gastrointestinal; HCC, hepatocellular cancer; miRNA, microRNA; PaC, pancreatic cancer.

Table 2 Compilation of p53-regulated miRNAs and their alterations in GI cancers

miRNA	Validated by	Clinical and pathological associations in GI cancers
miRNAs induced by p53		
miR-34a	Luc reporter (mut), qPCR, ChIP[24]	CRC: downregulated in tumors[38] and serum;[162] Downregulation in metastatic tumors;[70,163] CpG methylation[66,67] in metastatic tumors[70] EC, HCC: downregulated in tumors;[39,41] CpG methylation[39,41,164] GC: downregulated in tumors[40] PaC: downregulation associated with poor OS;[165] CpG methylation[66,67]
miR-34b/c	Luc reporter (mut), qPCR, ChIP[24]	CRC, GC, PaC: CpG methylation[67,69] EC: upregulation associated with advanced tumor stage;[166] CpG methylation[164] HCC: downregulated in tumors[41]
miR-15a/16-1	qPCR, ChIP[33]	CRC: miR-16-1 down-regulated in tumors;[77] Downregulation of miR-16-1 associated with pN, TNM stage, and poor OS[77] EC: miR-15a upregulated in tumors[167]
miR-200c/141	Luc reporter (mut), qPCR, ChIP[32]	CRC: downregulation of miR-200c is associated with poor OS;[168] miR-200c is downregulated in metastatic CRC;[169] miR-200c is upregulated in patient serum;[112,170] Upregulation in serum is associated with tumor stage, pN, metastasis, and prognosis;[109] CpG methylation[171] EC: miR-200c is upregulated in patient serum;[108] Upregulation in serum associated with poor RFS[108] GC: miR-141 is downregulated in tumors[172] HCC: miR-200c is downregulated in tumors;[173] Downregulation associated with poor RFS[174]
miR-200a/ 200b/429	Luc reporter (mut), qPCR, ChIP[32]	CRC: miR-429 is downregulated in tumors[175]; downregulation of miR-200a/429 is associated with poor OS;[168] CpG methylation[171] EC: miR-200a/b are upregulated in tumors[167,176] GC: miR-200a is downregulated in tumors[176] PaC: CpG hypomethylation and overexpression in tumors[177]
miR-107	Luc reporter (mut), qPCR, ChIP[36]	CRC: upregulation associated with metastasis and poor OS[117] EC: downregulated in tumors and serum[178] GC: upregulated in tumors; Upregulation associated with tumor invasion, stage, pN, and poor DFS and OS[119] PaC: CpG methylation[179]
miR-145	Luc reporter (mut), qPCR, ChIP[35]	CRC: downregulated in tumors[180,181] and patient stool samples;[182] Downregulation associated with tumor size[91] EC, GC, HCC, PaC: downregulated in tumors[88–90,173,183,184]
miR-192/ 194/215	qPCR, ChIP[34]	CRC: downregulation of miR-192/194/215 in tumors;[34,185,186] Downregulation of miR-192/215 associated with stage, grade, pN;[103,186] Downregulation of miR-215 associated with poor RFS;[101] Upregulation of miR-194 associated with poor RFS and OS[187] GC: downregulation of miR-194 associated with higher tumor size and stage;[188] miR-215 upregulated in tumors[189]
miR-29	Luc reporter, qPCR[149]	CRC: upregulated in serum;[190] Upregulation associated with metastasis and OS[191] GC: downregulated in tumors; Downregulation associated with metastasis[152,192] HCC: downregulated in tumors; Downregulation associated with poor RFS and OS[153,154]
miR-605	Luc reporter (mut), qPCR, ChIP[193]	NA
miR-149	Luc reporter (mut), qPCR, ChIP[194]	CRC: downregulated in tumors;[195] CpG methylation;[196] Downregulation associated with invasion and poor OS[196] GC: downregulated in tumors[197]
miR-22	Luc reporter (mut), qPCR, ChIP[198]	CRC: downregulated in tumors and liver metastases; Downregulation associated with poor OS[199] EC, PaC: upregulated in serum[200,201] GC: downregulated in tumors;[202] Downregulation associated with tumor stage, pN, metastasis, poor OS[203] HCC: downregulated in tumors, Downregulation associated with pN, grade, and poor OS[204,205]
miR-23b	Luc reporter (mut), ChIP[206]	EC: downregulation associated with poor prognosis[207] CRC, HCC: downregulated in tumors[208,209]
miR-205	Luc reporter (mut), qPCR, ChIP[210]	EC: downregulated in tumors,[211,212] Down-regulation associated with poor prognosis[207] HCC: downregulated in tumors[213]
miR-1246	Luc reporter (mut), qPCR, ChIP[214]	CRC: downregulated in tumors[215]; Upregulated in patient serum[216] EC: upregulated in tumors[217] and patient serum[218]
miR-1204	qPCR, ChIP[219]	NA

(*Continued*)

Table 2 (*Continued*)

miRNA	Validated by	Clinical and pathological associations in GI cancers
miRNAs repressed by p53		
miR-17-92	Luc reporter (mut), qPCR, ChIP[126]	CRC,[220,221] EC,[222,223] GC,[224,225] HCC,[226] PaC;[227] Upregulated in tumors
miR-224	Luc reporter (mut), qPCR, ChIP[124]	CRC: upregulated in tumors;[228,229] Upregulation associated with poor RFS and OS;[228,229] Downregulation associated with poor OS;[230] Upregulation associated with tumor size, stage, and metastasis[229] HCC: upregulated in tumors[231,232]
miR-502	Luc reporter[125]	CRC: downregulated in tumors[125]

Abbreviations: ChIP, chromatin immunoprecipitation; CRC, colorectal cancer; DFS, disease-free survival; EC, esophageal cancer; GC, gastric cancer; GI, gastrointestinal; HCC, hepatocellular cancer; Luc reporter, Luciferase miRNA promoter reporter assay; miRNA, microRNA; mut, mutation in the p53 binding site; NA, not applicable or not analyzed; OS, overall survival; PaC, pancreatic cancer; pN, nodal status; qPCR, quantitative real-time polymerase chain reaction; RFS, relapse-free survival; TNM, tumor, node, metastasis status based classification.

reduced proliferation and premature senescence. Therefore, p53 may operate as a checkpoint to monitor proper miRNA processing. Moreover, expression of *Dicer1* is regulated by the p53 family member p63, which can be inhibited by association with mutant p53.[30] Finally, p53 also affects miRNA target gene selection by regulating mRNA-binding proteins, such as RNA-binding-motif protein 38, which competes with miRNAs for binding to 3′-UTRs of mRNAs.[31] miRNAs transcriptionally induced by p53 include the miR-34,[21–26] miR-200,[32] miR-15a/16-1,[33] and miR-192/194/215[34] clusters, as well as miR-145[35] and miR-107.[36] Yet some of these miRNAs, such as miR-16-1, miR-145, and miR-199a-3p, are also regulated on the post-transcriptional level by p53.[28,37] The expression of the majority of these miRNAs is frequently altered in GI tumors and has been associated with clinical and pathological parameters of various types of GI cancer (Tables 1 and 2).

The miR-34 family

The miR-34 family includes three members – miR-34a, miR-34b, and miR-34c – which show a marked induction by p53.[8] MiR-34a is encoded by its own host gene, whereas miR-34b and miR-34c share a common precursor. Both *miR-34* genes contain several p53-responsive elements, which are occupied by p53 and mediate activation of miR-34a/b/c after DNA damage.[25,26] Expression of miR-34a/b/c is frequently downregulated in colorectal,[38] esophageal,[39] gastric,[40] and hepatocellular cancers (HCCs).[41] Consistently, all members of the miR-34 family were shown to suppress tumor growth and metastasis by inhibiting processes that promote cancer, including cell cycle progression, EMT, metastasis, and stemness and by promoting tumor suppressive processes, such as apoptosis and senescence.[42] MiR-34s regulate these processes through suppressing the expression of their target mRNAs, such as *SNAIL*, *c-Myc*, *Bcl2*, *c-Met*, and *Axl*.[43] The miR-34/p53 axis and its targets are often connected through positive or negative feedback loops that either reinforce the miR-34/p53 signaling or suppress it. For example, a positive feedback loop connects miR-34a and p53 via MDM4 (Figure 3A). MDM4 and its human counterpart HDM4 bind to p53 and inhibit its transcriptional activity. At the same time MDM4/HDM4 are targets of miR-34a.[44,45] Therefore, the repression of MDM4/HDM4 by miR-34a leads to stabilization of p53 and enhanced expression of miR-34a. Recently, it was shown that in addition to full-length HDM4 that is targeted by miR-34a, a short isoform of HDM4 also exists, which lacks seed-matching sites for miR-34a, thereby evading suppression by miR-34a.[45] Consistently, this short HDM4 isoform was highly expressed in tumors, where it presumably inhibits the miR-34a/p53 axis.

Furthermore, SIRT1 was shown to mediate activation of p53 by miR-34a.[46] SIRT1 is an nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase, which represses p53 activity by deacetylation of p53 protein. Yamakuchi et al showed that SIRT1 is a miR-34 target and that miR-34 induces the activity of p53 by repressing SIRT1 in colorectal cancer (CRC) cell lines (Figure 3B). Moreover, miR-34 not only represses the expression of SIRT1, but also suppresses SIRT1 activity by downregulating nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting enzyme of NAD^+ biosynthesis.[47] Furthermore, SIRT1 and MYC regulate each other via a positive feedback loop.[48,49] By repressing both SIRT1 and MYC, miR-34a may therefore efficiently suppress this circuitry.

Another double-negative feedback loop involving miR-34a was discovered by Siemens et al,[50] who demonstrated that miR-34a directly targets and suppresses the EMT-inducing transcription factor (EMT-TF) SNAIL, whereas SNAIL represses the *miR-34a* and *miR-34b/c* genes by directly binding to their promoters in CRC cell lines (Figure 3C). By utilizing HCC and CRC cells, Kim et al showed that p53 regulates EMT by inducing members of the miR-200

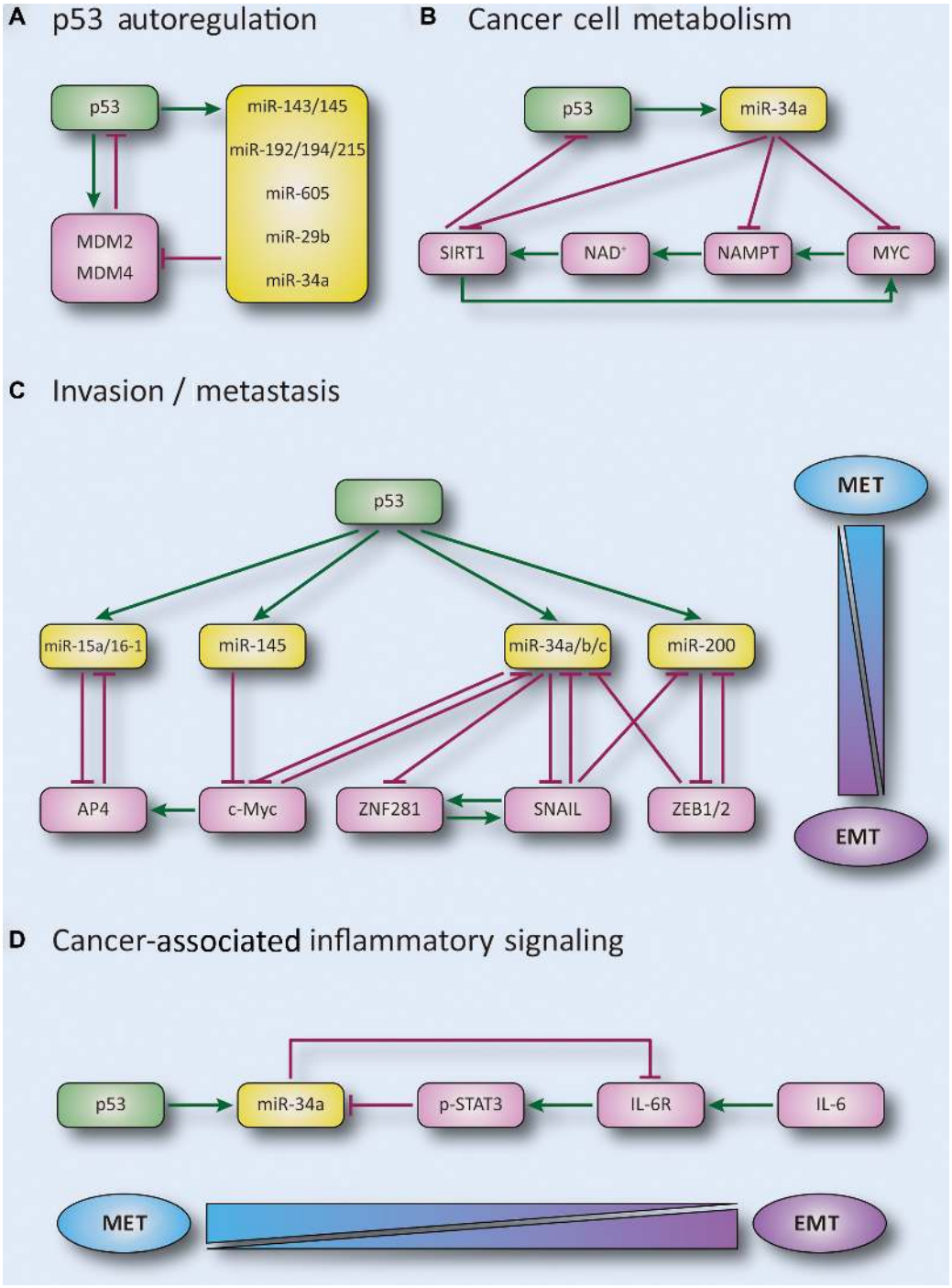

Figure 3 The role of p53/miRNA axis in (**A**) p53 autoregulation, (**B**) cancer cell metabolism, (**C**) invasion, and metastasis, as a result of the regulation of EMT/MET (**D**) cancer-associated inflammatory signaling.

Notes: Color code: p53/green; miRNAs/yellow; miRNA-targets/red; green arrow/activation; red arrow/inhibition.

Abbreviations: EMT, epithelial–mesenchymal transition; IL-6, interleukin 6; IL-6R, interleukin 6 receptor; MET, mesenchymal–epithelial transition; miRNA, microRNA; NAD^+, nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyltransferase.

family,[32] which also represent EMT-regulating miRNAs that suppress EMT by a similar double-negative feedback loop involving the EMT-TFs ZEB1 and ZEB2.[51,52] Thus, p53 is a key regulator of cellular plasticity by controlling EMT and its counterpart mesenchymal–epithelial transition (MET) through inducing the miRNAs of the miR-34 and miR-200 family (Figure 3C). These miRNAs form two double-negative feedback loops with their targets SNAIL, ZEB1, and ZEB2 that act as bimodal switches to stabilize either the epithelial or the mesenchymal state. Moreover, ZEB1

was also shown to repress miR-34a expression by binding to the same E-boxes in the *miR-34* promoters as SNAIL, thereby further interconnecting the miR-34/SNAIL and miR-200/ZEB loops.[50,53] In addition, we recently showed that the zinc-finger 281 (ZNF281) protein is an important miR-34 target with respect to EMT.[54] We found that the expression of ZNF281 is controlled by miR-34 and SNAIL in a coherent feed-forward-loop, whereby SNAIL and ZNF281 induce each other, whereas miR-34 can directly repress both SNAIL and ZNF281 (Figure 3C). Accordingly, ectopic SNAIL induced EMT by directly activating *ZNF281* and concomitantly repressing *miR-34a* expression, which leads to a further increase in ZNF281 levels. Notably, the induction of *ZNF281* by SNAIL was required for SNAIL-induced EMT.

Recently, we demonstrated that inflammation can suppress the expression of miR-34a.[55] We showed that exposure to the proinflammatory cytokine interleukin-6 (IL-6) results in repression of *miR-34a* via direct binding of the IL-6 effector STAT3 to the first intron of the *miR-34a* gene. Furthermore, we identified the IL-6 receptor (IL-6R) as a direct target of miR-34a. Further functional analysis revealed the existence of an IL-6R/STAT3/miR-34a feedback loop (Figure 3D). The activation of this loop was required for EMT, invasion, and metastasis of CRC cell lines and was associated with nodal and distant metastasis in CRC patients. Moreover, in *miR-34a*-deficient mice, colitis-associated intestinal tumors displayed activation of the loop and, in contrast to tumors in wild-type mice, progressed to invasive carcinomas. Our findings suggest that the activation of the IL-6R/STAT3/miR-34a loop by IL-6 drives cancer cells toward a mesenchymal and invasive phenotype, whereas suppression of the loop by p53 shifts cancer cells toward an epithelial state and prevents EMT and invasion.[55]

Reintroduction of miR-34 into tumors, which lost miR-34 expression, may represent an attractive alternative for cancer treatment. The most common approach for miRNA delivery relies on lipid-based nanoparticles, which contain vectors expressing miRNAs, or ~19–23-nt double-stranded mimics of mature miRNAs. These can be administered systemically by intravenous injection or locally into tumors. Several studies have shown that systemic miR-34a delivery suppresses tumor growth in vivo. Using xenograft or genetically engineered mouse models of melanoma, lymphoma, multiple myeloma, breast, prostate, pancreatic, and non-small-cell lung cancer, the authors observed an inhibition of tumor growth by 20% to 83% after reintroduction of miR-34a.[56] Importantly, no severe toxicity caused by systemic miR-34a delivery has been observed in mice.[57,58] Likewise, no unwanted immune response has been detected, based on serum cytokine levels in immune-competent mice.[59] Recently, the company Mirna Therapeutics has initiated a clinical Phase I trial of nanoparticle-based delivery of miR-34a in patients with non-resectable primary liver cancer or metastatic cancer with liver involvement.[60] Therefore, miR-34a may be one of the first miRNA mimics to reach the clinic. Conventional anticancer therapies, such as chemotherapy and treatment with radiation, induce miR-34 expression in human cancer cells with wild-type p53.[27] However, since the majority of human tumors lack normal p53 function, replacement of miR-34 may enhance the efficacy of standard cancer therapies. Indeed, in prostate, colorectal, and bladder cancer cells, reintroduction of miR-34a precursors enhanced the sensitivity toward camptothecin, paclitaxel, 5-fluorouracil, and cisplatin.[61–65] Furthermore, lentiviral transduction of miR-34a sensitized gastric and pancreatic cancer cells to radiation and to the chemotherapeutic drugs docetaxel, gemcitabine, cisplatin, and doxorubicin.[63,64] Moreover, we recently showed that c-Kit is an important miR-34a target that mediates, at least in part, chemosensitization by miR-34a in CRC cell lines.[65] Thus, these results suggest that combined treatment with miR-34 mimics may enhance the beneficial effects of conventional cancer therapies.

Downregulation of miR-34 expression in tumors has been frequently attributed to methylation of the CpG islands present in promoters of *miR-34a* and *miR-34b/c*.[66–69] CpG methylation is causally involved in repression of *miR-34-a/b/c*, since treatment of CRC cell lines with the demethylating agent 5-aza-2′-deoxycytidine leads to re-expression of *miR-34a/b/c*.[66,68,69] Moreover, a significant inverse correlation between *miR-34a* methylation and expression has been observed in colon tumors.[70,71] Therefore, miRNA cancer treatment strategies may rely not only on delivery of synthetic miRNA mimics corresponding to miR-34a/b/c into tumors, but also on re-expression of these miRNAs using demethylating agents. Indeed, treatment with BioResponse 3,3′-Diindolylmethane, an experimental anti-androgen prostate cancer drug, resulted in demethylation and re-expression of *miR-34a* in prostate cancer cells.[72] In a Phase II clinical trial, treatment of prostate cancer patients with BioResponse 3,3′-Diindolylmethane prior to radical prostatectomy led to the re-expression of *miR-34a* as well as repression and nuclear exclusion of its target, the androgen receptor.[72,73] Several reports showed that *miR-34* methylation may also have prognostic value. In our study, *miR-34a* methylation

in primary CRC was significantly associated with increased formation of lymph node and liver metastases.[70] Recently, Wu et al analyzed *miR-34a/b/c* methylation in stool samples of 82 CRC patients and 40 controls.[74] They demonstrated that detection of *miR-34a* and *miR-34b/c* methylation could identify CRC with a remarkable sensitivity of 76.8% or 95% and a specificity of 93.6% or 100%, respectively. Therefore, the detection of miR-34 miRNAs and CpG methylation of *miR-34* promoter regions in body fluids or stool represent potential biomarkers which may be utilized for noninvasive screening and diagnosis of cancer in the future.

miR-15a and miR-16-1

Mir-15a and miR-16-1 were the first miRNAs genetically linked to cancer: In 2002, Calin et al showed that *miR-15a* and *miR-16-1*, which are encoded within an intron of the *DLEU2* gene, are frequently deleted and/or downregulated in chronic lymphocytic leukemia.[75] Notably, a knockout of *DLEU2* or of the *miR-15a/16-1*-bearing intron in mice confirmed that loss of *miR-15a/16-1* causes chronic lymphocytic leukemia.[76] The expression of miR-15a and miR-16-1 is induced by p53 via transcriptional[33] and post-transcriptional mechanisms.[28] Several studies implicated the downregulation or loss of miR-15a and miR-16-1 expression in GI cancers. For example, the expression of miR-16-1 was significantly lower in primary CRC when compared to the corresponding normal colonic mucosa.[77] Moreover, decreased miR-16-1 expression was associated with lymph node metastasis and recurrence of colorectal tumors.[77] Furthermore, ectopic expression of miR-15a and miR-16-1 inhibited the proliferation of pancreatic and colorectal cancer cells[78,79] and led to a significant inhibition of subcutaneous growth of CRC cell lines in immune-compromised mice.[80] Interestingly, hepatitis B virus X protein, which is involved in the initiation and progression of HCC downregulates miR-15a/16 expression, suggesting that reintroduction of these miRNAs may be an effective treatment of hepatitis-B-virus-related chronic liver diseases.[81] MiR-15a and miR-16-1 act tumor suppressive, at least in part, by promoting apoptosis and cell cycle inhibition via targeting the anti-apoptotic protein Bcl2[82] and cell cycle regulators, including CDK6 and cyclin D1, respectively.[83,84] Recently, we demonstrated that miR-15a/16-1 also inhibit EMT, invasion, and metastasis of CRC cells by directly targeting the EMT-TF AP4.[85] Interestingly, AP4 itself is a repressor of the *DLEU2* gene. We showed that miR-15a/16-1 and the EMT-inducing factor AP4[86] form a double-negative feedback loop that stabilizes low expression of miR-15a/16-1 and elevated expression of AP4 in invasive CRC cells and tumors, thereby ultimately promoting CRC metastasis (Figure 3C).[85]

miR-145

p53 controls the expression of miR-145 by two mechanisms: first, p53 directly induces the transcription of the *miR-145* gene,[35] and second, p53 enhances miR-145 maturation via modulation of Drosha-mediated miRNA processing.[28,87] In line with a regulation by p53, expression of miR-145 is significantly lower in various tumors that harbor p53 mutations, including esophageal, gastric, pancreatic, colorectal, and bladder cancers.[88–92] Accordingly, ectopic miR-145 suppresses migration, invasion, and metastasis of gastric and colorectal cancer cells.[89,93] Moreover, therapeutic polyethylenimine-mediated reintroduction of miR-145 reduces proliferation and increases apoptosis of CRC cells in xenograft mouse models.[94] The tumor suppressing properties of miR-145 can be partially attributed to the repression of *MYC*, which represents a direct target of miR-145.[35] Similar to miR-34, miR-200, and miR-15a/16-1, miR-145 has also been shown to represent a mediator of p53-induced MET, the reversion of EMT (Figure 3C).[95] Another important oncogenic target of miR-145 is KRAS.[96] Interestingly, activated KRAS also represses miR-145 via RREB1, thereby forming a feed-forward loop that potentiates RAS signaling. Accordingly, loss of miR-145 is frequently observed in *KRAS* mutant pancreatic cancers, and restoration of these miRNAs inhibits tumorigenesis.[96] Xu et al showed that miR-145 negatively regulates the pluripotency factors OCT4, SOX2, and KLF4, and thereby represses self-renewal and induces differentiation of human embryonic stem cells.[97] Moreover, the same group reported that the *miR-145* promoter is bound and repressed by OCT4, thereby forming a negative feedback loop.[97] Loss of p53 leads to increased generation of induced pluripotent stem cells and expansion of cancer stem cells.[98] This effect might at least in part be due to the lack of p53-induced *miR-145* expression and consequent upregulation of OCT4. Finally, like miR-34a targets MDM4, miR-145 directly targets and represses the p53 inhibitor MDM2.[99] The result is another positive feed-forward loop that leads to stabilization of p53 and elevated expression of p53-induced miRNAs (Figure 3A).

The miR-192/miR-194/ miR-215 family

MiR-192, miR-194, and miR-215 are encoded by two clusters located at two different sites: The *miR-194-1/miR-215* cluster

on chromosome 1 (1q41) and the *miR-192/miR-194-2* cluster on chromosome 11 (11q13.1). Both clusters are directly induced by p53.[34,100] Interestingly, miR-194-1 and miR-194-2 have the same mature sequence, although they are derived from two different precursors on two chromosomal locations. MiR-192 and miR-215 have the same seed sequence, whereas the seed sequence of miR-194 differs. All three miRNAs display decreased expression in colorectal tumors.[34] Furthermore, low expression of miR-194 and miR-215 significantly correlates with a high probability of relapse and shorter survival in colorectal patients.[101] MiR-192, miR-194, and miR-215 regulate cell cycle progression and proliferation via the repression of functionally important targets, such as *CDC7, MAD2L1*, and *CUL5*.[102] Moreover, miR-192 suppresses liver metastasis of CRC cells by targeting *BCL2, ZEB2*, and *VEGF-A*,[103] while miR-194 inhibits EMT in endometrial cells by targeting *BMI-1*.[104] Importantly, similar to other p53-induced miRNAs, miR-192, miR-194, and miR-215 also directly target MDM2 and therefore interfere with the autoregulatory MDM2/p53 loop (Figure 3A).[100]

The miR-200 family

The two genes that give rise to the miR-200c/141 and the 200a/200b/429 miRNAs represent direct p53 target genes.[32] The members of the miR-200 family are tumor suppressing miRNAs and several studies showed that they play a crucial role in regulating the balance between EMT and MET by forming a double-negative feedback loop with their targets, the EMT-inducers ZEB1 and ZEB2 (Figure 3C).[52,105] Moreover, miR-200c also suppresses stemness by targeting the stem cell factors KLF4, SOX2, and the polycomb repressor BMI-1.[106,107] Several studies reported that elevated levels of cell-free, circulating miR-200c and miR-200a in the blood of colorectal, gastric, and esophageal cancer patients are associated with increased tumor stage, presence of metastases, and poor survival.[108–112] At first sight, this data seems contradictory, since functional studies showed that miR-200s repress EMT, invasion, and metastasis. Yet, recent studies showed that during the formation of metastases, cancer cells undergo MET and re-express EMT-suppressing genes and miRNAs.[113] Therefore, elevated levels of EMT-suppressing circulating miRNAs, such as miR-200c, might originate from metastases and indicate metastatic dissemination.

miR-107

The miRNA miR-107 is encoded by an intron of the p53-induced *pantothenate kinase 1 (PANK1)* gene.[36,114] Several studies showed that ectopic expression of miR-107 enhances EMT, migration, and promotes metastatic dissemination, whereas the loss of miR-107 represses migration and metastasis of colorectal, breast, and gastric cancer cells.[115–118] In line with these observations, expression of miR-107 is higher in gastric tumors compared with adjacent normal tissue.[119] Moreover, high expression of miR-107 correlates with lymph node and distant metastasis as well as poor survival of colorectal, breast, and gastric cancer patients.[115–120] The pro-metastatic properties of miR-107 are mediated by repression of its targets, the metastasis suppressors DAPK and KLF4.[117] Furthermore, Martello et al showed that miR-107 targets and represses DICER1, a key component of the miRNA processing machinery, thereby attenuating global miRNA production.[115] Therefore, elevated levels of miR-107 in tumors may contribute to the global reduction of miRNA abundance that was observed in various cancer types.[121] In addition to regulation of mRNA targets, miR-107 can also directly interact with and negatively regulate the let-7 miRNA.[116] Accordingly, miR-107 increased the tumorigenic and metastatic potential of human breast cancer cell lines in xenograft mouse models via inhibition of let-7 and upregulation of let-7 targets.[116] However, others have shown that miR-107 also has tumor suppressing functions by inhibiting cell proliferation and migration of breast cancer, gastric cancer, and glioma cells.[120,122,123] These tumor suppressing effects could be partially attributed to the miR-107-mediated repression of the response to hypoxia and angiogenesis via targeting of HIF 1β, resulting in a decreased supply of oxygen and nutrients and subsequent inhibition of tumor growth.[114] The decrease in functional HIF1α–HIF1β dimers after p53-mediated activation of miR-107 may suppress glycolysis under hypoxic conditions. These results indicate that p53-deficient tumors may be resistant to hypoxia not only because of decreased apoptosis and senescence, but also because of increased HIF1 signalling due to the decrease in miR-107 which results in metabolic and angiogenic adaptation. Altogether, the majority of the current data suggests that miR-107 is an oncogenic miRNA that promotes EMT, migration, and metastasis. However, these observations are at first sight not compatible with the induction of miR-107 by p53, which would be expected to mediate tumor suppressive functions. A possible explanation may be that p53 induces miR-107 and thereby downregulates DICER1 to limit the production of p53-induced miRNAs, which would otherwise lead to an unrestrained induction of p53 because of the positive feedback loops these often form with p53.

p53-repressed miRNAs

p53 also directly represses certain miRNAs, including miR-224,[124] miR-502,[125] and the miR-17-92 cluster.[126] However, this type of regulation seems to occur less frequently than the induction of tumor suppressive miRNAs by p53. As expected, miRNAs repressed by p53 mostly have oncogenic functions. The miR-17-92 primary transcript encodes the miRNAs miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a-1. The miR-17-92 clusters undergo genomic amplification and display elevated expression in various cancer entities, including colon cancer.[127] The miRNAs of the miR-17-92 family promote cell proliferation, increase angiogenesis, promote cell survival, and exhibit strong protumorigenic activities in multiple mouse tumor models.[128] Yan et al showed that miR-17-92 is repressed upon hypoxia via direct interaction of p53 with the *miR-17-92* promoter.[126] Due to the strong cell survival promoting properties of miR-17-92 family members, it is likely that the repression of *miR-17-92* expression by p53 plays a role in p53-induced apoptosis.

Regulation of p53 by miRNAs

p53 not only regulates the expression and processing of miRNAs, but is also under the control of certain miRNAs. Several miRNAs repress the translation of *TP53* mRNA by directly binding to its 3′-UTR (Tables 1 and 3). Since these miRNAs diminish the tumor suppressive activity of p53, they often represent oncomirs. Accordingly, they often exhibit elevated expression in tumors. Similar to the p53-regulated miRNAs the expression of p53-regulating miRNAs is frequently altered in GI tumors (Tables 1 and 3). The first miRNA that was characterized as a direct suppressor of p53 was miR-125b. Le et al. Showed that miR-125b is a negative regulator of p53 expression and p53-induced apoptosis during development and stress response.[129] Furthermore, it has been shown that miR-125 targets several

Table 3 Compilation of miRNAs that directly target p53 and their alterations in GI cancers

miRNA	Validated by	Clinical and pathological associations in GI cancers
miR-25	Luc reporter (mut), qPCR, WB[134]	CRC: upregulated in tumors; Upregulation associated with invasion, metastasis, poor OS[146] EC: upregulated in tumors and serum;[233] Upregulation associated with pN and tumor stage[137,145] GC: upregulated in serum[234] and tumors;[235] Upregulation associated with tumor progression[236,237]
miR-30d	Luc reporter (mut), qPCR, WB[134]	CRC, PaC: gene amplification[148] HCC: upregulated in tumors; Upregulation associated with metastasis[238]
miR-33	Luc reporter (mut), WB[135]	NA
miR-98	Luc reporter (mut), WB[143]	EC: downregulated in tumors; Downregulation associated with tumor stage and pN[239]
miR-125a	Luc reporter (mut), WB[142]	EC: downregulation associated with tumor progression[240] GC: downregulation associated with invasion, metastasis, poor OS[240–242] HCC: downregulated in tumors; Downregulation associated with tumor stage and metastasis[243,244]
miR-125b	Luc reporter (mut), WB[129]	CRC: upregulation associated with tumor size, invasion, poor OS[241] EC: downregulation associated with tumor progression[240] GC: upregulation associated with tumor progression;[236] Downregulation associated with tumor progression[240] HCC: upregulated in serum;[131] Downregulated in tumors[244,245] PaC: upregulated in tumors[246]
miR-150	Luc reporter (mut), WB[138]	CRC: downregulated in tumors; Downregulation associated with poor OS[247] EC: downregulated in tumors; Downregulation associated with invasion, metastasis, and poor OS[248] GC: upregulated in tumors[249] PaC: downregulated in tumors[250]
miR-214	Luc reporter (mut), WB[141]	CRC: upregulation associated with poor OS[236] EC: upregulated in tumors;[251] Downregulated in tumors[239] GC: upregulated in tumors; Upregulation associated with poor OS[252] HCC: downregulated in tumors; Downregulation associated with poor RFS and OS[253–255] PaC: upregulated in tumors[78]
miR-375	Luc reporter (mut), WB[139]	EC: downregulated in tumors and serum; Downregulation associated with poor OS[145] PaC: downregulated in tumors[236]
miR-380	Luc reporter, WB[136]	NA
miR-504	Luc reporter (mut), WB[133]	NA
miR-1285	Luc reporter (mut), qPCR, WB[140]	NA

Abbreviations: CRC, colorectal cancer; EC, esophageal cancer; GC, gastric cancer; GI, gastrointestinal; HCC, hepatocellular cancer; Luc reporter, Luciferase reporter assay with *p53* 3′-UTR; miRNA, microRNA; mut, mutation in the miRNA seed sequence; NA, not applicable or not analyzed; OS, overall survival; PaC, pancreatic cancer; pN, nodal status; qPCR, quantitative real-time polymerase chain reaction; RFS, relapse free survival; WB, Western blot.

additional components of the p53 network, which include both regulators of apoptosis like Bak1, Igfbp3, Itch, Puma, Prkra, Tp53inp1, and Zac1, and components of the cell cycle machinery such as cyclin C, Cdc25c, Cdkn2c, Edn1, Ppp1ca, and Sel1l.[130] The authors proposed that by regulating proliferative and apoptotic genes, miR-125b buffers and fine-tunes the activity of the p53 network in order to control the balance between proliferation and apoptosis. Recently, it was shown that the levels of miR-125b are significantly higher in the serum of patients with hepatitis-B-virus-positive HCC and therefore circulating miR-125b may represent a potential non-invasive marker for HCC.[131] Moreover, elevated expression of miR-125 was also associated with increased tumor size, enhanced invasion, and poor prognosis in CRC patients.[132] Another miRNA that negatively regulates p53 expression via two seed-matching sequences in the human *TP53* 3′-UTR is miR-504.[133] Accordingly, ectopic expression of miR-504 reduced p53 protein levels and impaired p53 functions, especially p53-mediated apoptosis and G1-arrest in response to stress. Furthermore, ectopic expression of miR-504 promoted tumorigenicity of colon cancer cells in mice.[133] Additionally, miR-25, miR-30d, miR-33, miR-98, miR-150, miR-214, miR-375, miR-380, and miR-1285 also downregulate p53 protein levels through seed-matching sequences in the 3′-UTR of *TP53*.[134–144] Accordingly, ectopic expression of these miRNAs suppresses p53 expression and induces phenotypes that are consistent with a decrease in p53 function, such as reduced apoptosis and senescence, and increased invasion and stem cell self-renewal.[134–137] miR-25 levels were increased in esophageal tumors and serum of esophageal cancer patients displayed elevated levels of circulating miR-25.[145] Moreover, expression of miR-25 was significantly higher in colorectal tumors and elevated levels of miR-25 were associated with increased tumor invasion, lymph node metastasis, distant metastasis, TNM (tumor, node, metastasis status based classification) stage, and poor survival of CRC patients.[146] MiR-30d is an important regulator of autophagy,[147] and interestingly, amplification of the *MIR30D* gene was found in ~30% of 1,283 analyzed solid tumors, including bladder, colorectal, and pancreatic cancer.[148]

In addition to the direct repression of p53 by miRNAs, several miRNAs also regulate the expression of p53 indirectly. As described above, the expression of the p53 inhibitors MDM2 and MDM4 is directly repressed by several p53-induced miRNAs: MDM2 is a target of miR-145, miR-192/194/215, miR-605, and miR-29b, whereas MDM4 is targeted by the miR-34 family members (Figure 3A). Therefore, p53-mediated induction of these miRNAs results in a positive feedback and enhanced p53 activation. In addition, miRNAs of the miR-29 family target the expression of other negative regulators of p53, such as Cdc42, PPM1D, and the regulatory subunit of phosphatidylinositol-3 kinase (PI3K), p85α, and thereby indirectly enhance the levels and activity of p53.[149,150] In addition, *miR-29* is also directly induced by p53,[149] thereby forming a positive feedback loop that is activated during aging and DNA damage, and reinforces p53 effector functions, such as apoptosis and senescence. The members of the miR-29 family are aberrantly expressed in various tumors, including gastric cancer and HCC.[151–153] Moreover, low expression of miR-29 in HCC was associated with decreased survival.[154] Furthermore, miR-122, which is expressed exclusively in the liver, is frequently downregulated in liver cancer.[155] It was shown that miR-122 stabilizes and therefore increases p53 protein levels and activity via downregulation of its target cyclin G1.[156] Repression of cyclin G1 results in decreased recruitment of the PP2A phosphatase to the p53-inhibitor MDM2. The resulting decrease in MDM2 activity leads to activation of p53.[157] Interestingly, *Cyclin G1* is also directly induced by p53 and therefore forms a negative feedback loop with p53.[158] However, therapeutic treatment with miR-122 mimtics might abrogate this loop by downregulation of cyclin G1. Indeed, it has been shown that ectopic miR-122 expression increases the sensitivity of HCC cell lines to the chemotherapeutic agent doxorubicin, which is known to induce p53.[156] However, it should be noted that miR-122 increases chemosensitivity also in the absence of wild-type p53 and therefore seems to have p53-independent functions.

Conclusion and outlook

Although numerous links between p53 and miRNAs have been identified, we have only begun to understand the complex interplay between p53 and miRNAs in tumor suppression. Therefore, additional efforts are necessary to uncover more details of the p53/miRNA network. Since p53 has many functions in tumor suppression, future research should focus on identifying which miRNA is responsible for mediating specific p53 functions. It would also be of interest to investigate whether the complete spectrum of tumor suppressing functions of p53, which is frequently lost in tumors, can be restored by the introduction of specific combinations of p53-induced miRNAs. So far, the majority of studies have rather focused on the identification and characterization of single p53-regulated miRNAs.

A feasible strategy for a comprehensive, genome-wide identification of p53-regulated miRNAs and their target genes has been recently described by us.[159] This strategy employs a combination of various unbiased genome-wide next generation sequencing screens to simultaneously identify and characterize p53-regulated miRNAs and their targets. By now, knockout mouse models of single p53-induced miRNAs have not fully recapitulated the cancerous phenotype of p53 knockout mice, which is characterized by the early onset of lymphomas.[160] Therefore, it would be interesting to generate genetically modified mice that simultaneously lack multiple p53-related miRNAs to investigate whether loss of certain combinations of miRNAs fully or at least partially mimics the phenotype of p53-knockout mice. Complementarily, *p53* knockout mice could be treated with a cocktail of p53-induced miRNAs to investigate whether certain combinations of miRNAs can suppress the tumor promoting effects of p53 loss. In light of the central role of p53-regulated miRNAs or p53-regulating miRNAs for tumor suppression, the introduction of these miRNAs or of miRNA antagonists into tumor cells represents an exciting possibility for novel cancer-therapeutic approaches. Such therapies could also be performed in combination with standard anticancer therapies as has been already shown for miR-34a, which sensitized gastric cancer cells to the chemotherapeutic drugs docetaxel, gemcitabine, cisplatin, and doxorubicin.[63] A major obstacle for such approaches is the currently low efficiency of miRNA delivery into tumor cells. Therefore, further research is needed to develop more efficient strategies for *in vivo* miRNA delivery. Promisingly, improved delivery using novel nanoparticles was recently employed to show that a combination of miR-34a mimics and siRNAs directed at mutant oncogenes is more effective than either RNA alone in a pre-clinical mouse model of lung cancer.[161] Since p53-regulated miRNAs are often inactivated by CpG methylation in tumors, establishment of routine protocols for detection of methylation of selected promoters of miRNA-encoding genes in body fluids may represent an important aspect of future GI cancer diagnostics.

Disclosure

The authors report no conflicts of interest in this work.

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