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REVIEW

A Systemic Review on the Regulatory Roles of miR-34a in Gastrointestinal Cancer

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Abstract: MicroRNAs (miRNAs) are a class of endogenous non-coding single-stranded small-molecule RNAs that regulate gene expression by repressing target messenger RNA (mRNA) translation or degrading mRNA. miR-34a is one of the most important miRNAs participating in various physiological and pathological processes. miR-34a is abnormally expressed in a variety of tumors. The roles of miR-34a in gastrointestinal cancer (GIC) draw lots of attention. Numerous studies have demonstrated that dysregulated miR-34a is closely related to the proliferation, differentiation, migration, and invasion of tumor cells, as well as the diagnosis, prognosis, treatment, and chemo-resistance of tumors. Thus, we systematically reviewed the abnormal expression and regulatory roles of miR-34a in GICs including esophageal cancer (EC), gastric cancer (GC), colorectal cancer (CRC), hepatocellular carcinoma (HCC), pancreatic cancer (PC), and gallbladder cancer (GBC). It may provide a profile of versatile roles of miR-34a in GICs.

Keywords: miR-34a, gastrointestinal cancer, proliferation, migration, prognosis

Introduction

GICs are the most common malignant tumors in the world, including EC, GC, CRC, HCC, GBC, PC, etc. The incidence and mortality of GICs are extensively high. Recent studies have shown that the incidence and mortality of EC, GC, HCC, CRC, and PC rank among the top ten of malignant tumors in the Chinese population.[1,2] Moreover, EC, GC, HCC, and CRC are four leading causes of cancer deaths, accounting for about 60% of all cancer deaths.[1,2] At present, GICs are commonly treated with surgeons, chemical drugs, radiation therapy, and/or immunotherapy. However, the therapeutic responses are still limited. Therefore, it is of great significance to find new strategies to treat GICs.

miRNAs are non-coding single-stranded small-molecule RNAs with about 20–25 nucleotides in length.[3–5] miRNAs regulate target gene expression through complete or incomplete complementarity with the 3′-untranslated region (3′-UTR) of target mRNA to inhibit or degrade the target mRNA, thereby participating in a series of biological processes including cell proliferation and apoptosis, hematopoiesis process, fat metabolism, development, and so on.[6–8] miR-34a is one of the most closely concerned miRNAs and is widely expressed in various tissues including brain,[9] myocardium,[10] lung,[11] and liver.[12] However, miR-34a is abnormally expressed in a variety of tumors. For instance, miR-34a is down-regulated in breast cancer, prostate cancer, glioblastoma, EC, HCC and the other solid tumors, but it is up-regulated in chronic lymphoblastic leukemia[13–16] (Table 1). miR-34a is directly

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Table 1 miR-34a Expression in GICs

Cancer	Population	Paired		Unpaired	*P* value	Sample size	Assay	References
		Up	Down			(Tumor/Non-Tumor)		
EC	Kazakh	2	23	Down	0.0071	25/25	qPCR	[33]
	Chinese	2	6			8/8	qPCR	[34]
	Iranian			Down	<0.001	25/25	qPCR	[35]
	Chinese			Down	<0.0001	119/119	Microarray	[36]
GC	Chinese	4	8			12/12	qPCR	[50]
	Chinese			Down	<0.05	20/10	qPCR	[51]
	Chinese			Down	<0.001	62/20	qPCR	[52]
	Japanese			Down	0.024	280/120	Microarray	[53]
CRC	American			Up	<0.001	159/159	qPCR	[86]
	Chinese			Up	<0.001	113/113	qPCR	[86]
	Chinese	72	37			109/109	qPCR	[87]
	Hungarian			Up	<0.05	20/20	Microarray	[88]
	Italian	15	5			20/20	Microarray	[89]
	Chinese			Down	<0.05	25/15	qPCR	[90]
	Chinese			Down	<0.01	30/30	qPCR	[91]
	American			Down	0.002	10/10	qPCR	[94]
	Iranian			Down	0.004	63/45	qPCR	[92]
	Hungarian			Down	<0.001	43/12	qPCR	[93]
HCC	Chinese			Down	<0.001	11/9	qPCR	[131]
	Chinese			Down	<0.05	60/60	qPCR	[130]
	Chinese			Down	0.026	30/30	qPCR	[132]
	Chinese			Down	<0.00001	78/88	Microarray	[133]
	American			Down	<0.00001	73/73	Microarray	[133]
	Japanese			Down	<0.00001	96/96	Microarray	[133]
	Indian			Down	<0.00001	4/8	Microarray	[133]
PC	Chinese			Down	<0.001	159/82	qPCR	[153]
	Japanese			Down	<0.001	139/139	qPCR	[154]
	Brazilian			Up	0.001	24/10	qPCR	[155]
	American			Up	<0.05	42/7	Microarray	[156]
	American			Up	<0.05	36/36	Microarray	[177]
GBC	Chinese			Down	<0.05	77/36	qPCR	[173]

regulated by p53, and is inactivated by CpG methylation in a wide range of cancers.[16,17] A number of studies have demonstrated that miR-34a plays pivotal roles in cell proliferation, differentiation, migration, invasion, and survival by regulating a number of target genes involved in the mitogen-activated protein kinase (MAPK)/RAS proto-oncogene, GTPase (RAS), WNT/β-catenin, and the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathways in GICs[13,18,19] (Table 2 and Figure 1). Thus miR-34a showed potent anti-tumor activity and contributed to chemotherapy in GICs (Table 3).

Recently, more and more studies on miR-34a had been reported. Although several research groups have reviewed miR-34a from different sides,[13,18,20-29] the roles of miR-34a in GICs have not yet been systematically reviewed. Here, we present a global review of miR-34a in GICs.

miR-34a in EC

EC seriously threats human health with high morbidity and mortality.[30] EC is mainly divided into esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma, and undifferentiated carcinoma. In China, ESCC is a main type of EC with the highest incidence.[31] The average five-year survival rate of ESCC is only about 10%, indicating defects in its treatment and prognosis.[32] Therefore, it is necessary to ascertain the molecular mechanism and possible prognostic biomarkers of EC. At present, a lot of studies have focused

Table 2 The Targets of miR-34a identified in GICs

Cancer	Function			References
	Proliferation and Differentiation	Migration and Invasion	Treatment and Chemoresistance	
EC	BCL2, CCND1, CCNE2, CDK4, CDK6, E2F3, MYCN, PLCE1, SIRT1	FNDC3B, MMP2, MMP9, YY1		[17,37,38,44,45]
GC	MET, PCBP2, PDGFR, SIRT7	CDK6, E2F3, MYC, TGIF2	HK1, MET	[51,52,54–56,60,61,69,71,75]
CRC	E2F5, FMNL2, HMGB1, CDK4, CDK6, CCNE2, E2F3, BCL2	IL-6R, JAG1, NOTCH1, SIRT1, STAT3, SNAIL, ZEB1, SLUG, ZNF281, MET	BCL2, E2F3, LDHA, NOTCH1, NOTCH2, SIRT1, SMAD4, ATG4B, DAPK1, SP1	[97–99,102–110,112–118]
HCC	FOXM1, HDAC1, MYC, TLR4	MET, SNAIL	BCL2	[130,135,138,140,144,148]
PC	NOTCH1, XIST, CD44, CDK6	SLUG, SNAIL, ZEB1	BCL2, CCND1, E2F1, MYC, SIRT1	[154,159,161–163,166–168]
GBC	PNUTS			[173]

on the regulatory roles of miR-34a in the proliferation, differentiation, migration, invasion, and prognosis of EC.

miR-34a Expression in EC

To investigate relationship between miR-34a expression and the progression of EC, the expression of miR-34a in 78 EC tissues and 25 pairs of EC and non-tumor esophageal tissues was examined by Cui et al.[33] They found that the levels of miR-34a in 92% (23/25) of tumor tissues were significantly lower than those in non-tumor tissues. Moreover, the low-expression of miR-34a is closely related to the progression of EC. This is consistent with a previous study demonstrating that miR-34a is down-regulated in randomly selected 8 human EC tissues.[34] Down-regulation of miR-34a was further confirmed in another study, in which miR-34a expression in 50 EC tissues was measured and the down-regulated miR-34a was correlated with clinical pathology.[35] In addition, the results obtained from the Gene Expression Omnibus (GEO) database (accession number: GSE43732) showed a significant decrease in miR-34a levels in EC tissues compared with non-tumor tissues.[36] These studies provide evidences to show that miR-34a is down-regulated in EC, and is closely related to the progression of EC.

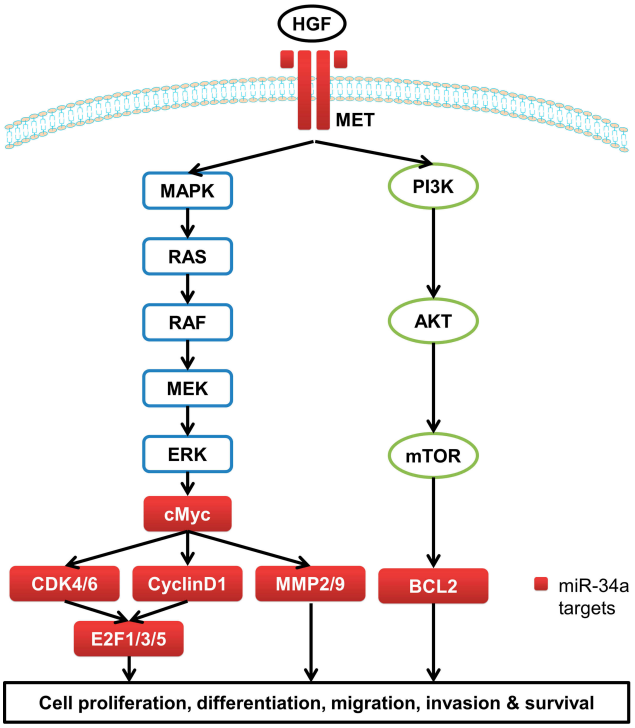

Figure 1 The target genes of miR-34a involved in MAPK/RAS and PI3K/AKT pathways.

The Role of miR-34a in the Proliferation and Differentiation of EC

There is a close relationship between abnormal expression of miR-34a and the proliferation and differentiation of EC. To explore the role of miR-34a in the development of EC, Shi et al[34] investigated the expression level and DNA methylation of miR-34a in EC samples. They found that miR-34a was down-regulated in EC, and the low-expression of miR-34a was related to the abnormal CpG methylation of its promoter. miR-34a induced apoptosis

Table 3 miR-34a-Based Treatment and Chemoresistance in GICs

Cancer	Treatment/ Chemoresistance	Strategies	Cell Line	In vivo/In vitro	Administration, Dosage, and Period	Result	References
EC	Treatment	Combined use of doxorubicin-loaded poly(ε-caprolactone) (PCL)-Pluronic micelles and miR-34a mimics	ECa-109	In vivo	Intravenous injection (5 mg/kg) Once every 3 days, 5 times	Enhanced anti-tumor effect	[47]
GC	Chemoresistance	*miR-34a mimics*	SGC-7901	In vitro		Increased the sensitivity of cells to DDP	[75]
	Treatment	Poly-L-lysine-graft-imidazole (PLI)/miR-34a mimics complex encapsulated in polyethylene glycol (PEG) liposome vesicles	MKN-74	In vivo	Intravenous injection (1 nmole of miR-34a) 2 times per week, 3 weeks	Enhanced the delivery efficiency of miR-34a	[76]
	Chemoresistance	miR-34a agomir	BGC-823	In vivo	Intratumoral injection (5 nM miR-34a+10 mg/kg luteolin) 2 times per week, 2 weeks	Enhanced the sensitivity of cells to luteolin	[52]
CRC	Treatment	Increased the levels of endogenous miR-34a	HCT8	In vitro		Spica prunellae exerted antitumor activity	[125]
	Chemoresistance	miR-34a mimics	HT29	In vitro		Increased sensitivity of cells to oxaliplatin	[122]
	Chemoresistance	pre-miR-34a	DLD-1	In vitro		Increased sensitivity of cells to 5- fluorouracil	[123]
	Chemoresistance	Increased the levels of endogenous miR-34a	HCT116, SW480	In vivo	siKCNQ1OT1 and siNC were inoculated subcutaneously in the right flank of the nude mice. (measured per week for 5 weeks)	Increased sensitivity of cells to oxaliplatin	[126]
	Chemoresistance	Increased the levels of endogenous miR-34a	HCT116, SW620	In vitro		Increased sensitivity of cells to oxaliplatin or 5- fluorouracil	[94]
	Treatment	Increased the levels of endogenous miR-34a	DLD-1	In vitro		Resveratrol exerted antitumor activity	[124]

(*Continued*)

Table 3 (Continued).

Cancer	Treatment/ Chemoresistance	Strategies	Cell Line	In vivo/In vitro	Administration, Dosage, and Period	Result	References
HCC	Chemoresistance	miR-34a mimics	Huh-7	In vitro		Sensitized the cells to sorafenib treatment	[148]
	Treatment	miR-34a mimics and erlotinib	HepG2	In vitro		Enhanced anti-tumor effect	[149]
PC	Treatment	miR-126 and miR-34a (AdCEAp-miR126/34a)	Panc-1	In vivo	Intratumoral injection (2×10^8pfu/dose) once every other day, 5 times	Enhanced anti-tumor effect	[167]
	Treatment	miR-34a mimics and PLK1 siRNA	MiaPaCa-2	In vivo	Intravenous injection (3 mg/kg) 5 consecutive times, 2 cycles with a 3 days break between them	Enhanced anti-tumor effect	[168]
	Treatment	A lipid-based nanoparticle for systemic delivery of miR-34a	MiaPaCa-2	In vivo	Intravenous injection (50 ug of DNA complexed with liposome at a 4:1 lipid/DNA charge ratio) 3 times per week, 3 weeks	Enhanced the delivery efficiency of miR-34a	[166]

and G0/G1 phase arrest by targeting several cell cycle genes or oncogenes, such as cyclin D1 (CCND1), cyclin E2 (CCNE2), cyclin dependent kinase 4 (CDK4), cyclin dependent kinase 6 (CDK6), E2F transcription factor 3 (E2F3), B cell lymphoma 2 (BCL2), sirtuin1 (SIRT1), and V-myc avian myelocytomatosis viral related oncogene (MYCN).[17,37,38] The genes CCND1, CCNE2, CDK4, CDK6 and E2F3 are mainly related to the cell cycle. They participate in the G1-to-S phase transition of the cell cycle. miR-34a disrupts cell cycle by binding to the 3′-UTR of these target genes. Since the genes BCL2, SIRT1, and MYCN are mainly related to cell senescence and apoptosis, miR-34a impacts cell proliferation and senescence by binding to their 3′-UTRs. Therefore, low-expression of miR-34a promoted the proliferation and anti-apoptosis of EC cells, and consequent progression of EC. In addition, miR-34a also affected the proliferation and differentiation of EC by targeting phospholipase C (PLCE1).[33] PLCE1 is a novel subtype of the PLC family, encoding phospholipase C enzyme, which regulates cell proliferation and differentiation through hydrolyzing membrane phosphatidylinositol 4, 5 diphosphate (PIP2) and producing inositol triphosphate (IP3) and diacylglycerol (DAG).[39,40] miR-34a inhibited PLCE1 expression by directly binding to PLCE1 3′-UTR. Thereby, the repressed PLCE1 promoted cell apoptosis, inhibited cell migration and enhanced the anti-tumor activity of miR-34a. However, low-expression of miR-34a in EC resulted in over-expression of PLCE1 and promotion of proliferation and migration of EC cells. These findings suggest that abnormal expression of miR-34a promotes the progression of EC by regulating target genes related to cell cycle, apoptosis, and senescence.

The Role of miR-34a in the Migration and Invasion of EC

Recent studies have found that methylation of miR-34a CpG island mediated miR-34a silencing contributes to the development of human EC. Specific DNA methylation markers at miR-34a CpG site were associated with EC metastasis.[41,42] Higher methylation of miR-34a CpG locus resulted in higher risk of EC metastasis. Furthermore, low-expression of miR-34a led to upregulation of its target genes, such as matrix metalloproteinase-2 (MMP2), matrix metalloproteinase-9

(MMP9), type III fibronectin domain protein 3B (FNDC3B), and nuclear transcription factor Yin Yang 1 (YY1), thereby promoting the migration and invasion of EC cells. In these genes, MMP2 and MMP9 are involved in cancer invasion and metastasis by degrading type IV collagen, and FNDC3B and YY1 participate in the process of cell proliferation and differentiation. In addition, miR-34a promoted the metastasis and invasion of ESCC through epigenetic mechanisms. Previous studies have shown that long non-coding RNA (lncRNA) MNX1-AS1 is significantly up-regulated in ESCC, and high-expression of MNX1-AS1 is related to lymph node metastasis in ESCC. miR-34a is a direct target of MNX1-AS1. Knockdown of MNX1-AS1 enhanced miR-34a expression. Reinforced miR-34a inhibited cancer cell migration through suppression of MNX1-AS1, indicating that miR-34a is an important downstream effector of MNX1-AS1 in ESCC cell migration.[43] These studies provided evidences to demonstrate that miR-34a inhibited migration and invasion of EC cells.[44,45]

The Role of miR-34a in the Prognosis of EC

Consistent results have shown that miR-34a is significantly down-regulated in 111 EC tissues, and the low-expression of miR-34a is related to the degree of tumor differentiation, lymph node status, and clinical stage.[42,46] Meanwhile, Kaplan-Meier analysis and Log rank test showed that miR-34a expression was reversely correlated with the overall survival of patients with EC. Multivariate COX (proportional hazards model) regression analysis showed that miR-34a expression was an independent prognostic factor for EC. Moreover, methylation of miR-34a CpG sites was negatively correlated with miR-34a expression, and hypermethylation of miR-34a CpG sites was significantly associated with advanced stage (III/IV) and lymph node metastasis in EC. These results indicate that miR-34a has important clinical significance and prognostic value in EC and it may be considered as a potential biomarker for the prognosis of EC.

The Role of miR-34a in the Treatment of EC

At present, few studies on the relationship between miR-34a and the treatment and chemotherapy resistance of EC were exerted. Dai et al established a new therapeutic strategy that combines doxorubicin-loaded poly(ε-caprolactone) (PCL)-Pluronic micelles and miR-34a to combat EC.[47] In vitro and in vivo combination of doxorubicin-loaded PCL-pluronic micelles and miR-34a achieved a significantly synergistic therapeutic effect over the single treatment, suggesting that miR-34a can be used to improve the anti-cancer activities of chemical drugs in the treatment of EC. However, studies on the roles of miR-34a in the treatment of EC are still needed to be further investigated.

miR-34a in GC

GC is the fourth most common cancer in the world with a high mortality rate and a low 5-year survival rate.[48] In China, the incidence of GC is the highest in GICs, and is the second in malignant tumors.[49] Recently, more and more studies have revealed important role of miR-34a in the proliferation, differentiation, migration, invasion, treatment, and prognosis of GC.

miR-34a Expression in GC

At present, studies have revealed that miR-34a is abnormally expressed in GC. For instance, Wu et al[50] detected the expression level of miR-34a in 12 pairs of primary GC tissues and adjacent non-tumor tissues by using quantitative real-time PCR (qPCR) method. The results showed that miR-34a expression was decreased in 66.7% (8/12) cancer tissues compared with non-tumor tissues. The average expression level of miR-34a in the GC tissues was lower than that in the normal tissues. Meanwhile, several studies also confirmed that miR-34a was down-regulated in GC tissues, and was associated with tumor size, cell differentiation, distant metastasis, lymph node metastasis, recurrence and tumor lymph node metastasis (TNM) staging in patients with GC.[51,52] Additionally, the results obtained from the Cancer Genome Atlas (TCGA) database demonstrated that low-expression of miR-34a was correlated with worse clinical outcome in GC patients.[53] These findings indicate a positive relationship between abnormal expression of miR-34a and the development of GC.

The Role of miR-34a in the Proliferation and Differentiation of GC

Recent studies have shown that miR-34a inhibits the proliferation of GC cells by suppressing platelet-derived growth factor receptor (PDGFR) and mesenchymal epithelial cell transformation (MET) through PI3K/AKT pathway.[54–56] miR-34a directly bond to PDGFR 3′-UTR and inhibited PDGFR expression in GC. The decreased expression of PDGFR led to repression of tumor angiogenesis and inhibition of the proliferation and differentiation of tumor cells. Since miR-34a is lowly expressed in GC, PDGFR is highly expressed, resulting in enhancement of the proliferation and migration of GC cells. Polycytosine binding protein 2 (PCBP2), an RNA-

binding protein, is an oncogenic protein and is highly expressed in GC.[57–59] Hu et al found that PCBP2 promoted GC growth by inhibiting the expression of miR-34a.[60] PCBP2 inhibited the apoptosis of GC cells by inhibiting the expression of miR-34a, and maintained the survival of GC cells, thereby promoted the development of GC. Another study reported that SIRT7 promoted the growth of GC cells and inhibited the apoptosis of GC cells by down-regulating the level of miR-34a.[61] SIRT7, a NAD1-dependent class III histone deacetylase, binds to the promoter of miR-34a and deacetylates H3K18ac, thereby inhibiting the expression of miR-34a. As a result, the down-regulation of miR-34a inhibited the apoptosis of GC cells and restored the proliferation ability of GC cells, and consequently promoted the proliferation and differentiation of GC. These findings provide a new perspective for the mechanism explaining miR-34a-inhibited proliferation and differentiation of GC.

The Role of miR-34a in the Migration and Invasion of GC

It has been shown that GC inhibitor Gastrokine 1 (GKN1) inhibits the migration and invasion of GC cells by down-regulating Ras homolog gene family member A (RhoA).[62] GKN1 inhibited epithelial-mesenchymal transition (EMT) by repressing the production of reactive oxygen species and PI3K/AKT signaling, as well as nuclear factor kappa-B (NF-κB)-dependent MMPs.[63,64] RhoA, a key member of the Rho family of small GTP-binding proteins, is a major regulator of actin-dependent cell contraction and cell motility, and is closely linked to the signaling pathways involved in cell proliferation and migration.[65–68] Further investigation demonstrated that the expression of miR-34a was positively correlated with the expression of GKN1, which was negatively correlated with RhoA. GKN1 also inhibited the expression of V-Myc avian myelocytomatosis viral oncogene homolog (c-Myc) in GC, which is a direct target of miR-34a.[69] GKN1-induced miR-34a inhibited the expression of c-Myc by binding to its 3′-UTR. However, c-Myc is an important transcription factor of RhoA.[70] Down-regulation of c-Myc expression inhibited RhoA expression, which in turn inactivated the PI3K/AKT signaling pathway and consequent EMT process, as well as the migration and invasion of GC cells. In addition, miR-34a also inhibited the migration and invasion of GC cells by targeting oncogenes TGIF2, E2F3, and/or CDK6.[51,71] These findings suggest that miR-34a plays a key role in the development of GC and can be considered as a therapeutic target for blocking metastasis and invasion of GC cells.

The Role of miR-34a in the Diagnosis and Prognosis of GC

It is reported that miR-34a is closely related to the diagnosis and prognosis of GC. Zhang et al[72] showed that the down-regulation of miR-34a in GC was associated with high occurrence rate and low overall survival of patients with GC. Another study showed that the expression of miR-34a was found to be closely related to tumor size, cell differentiation, distant metastasis, lymph node metastasis, and occurrence of GC.[73,74] Down-regulation of miR-34a was associated with Lauren grading and was positively correlated with overall survival of GC patients. Meanwhile, multivariate Cox regression analysis showed that miR-34a expression was an independent prognostic indicator of GC. These discoveries suggest that miR-34a may be used as a diagnosis and prognostic indicator for GC.

The Role of miR-34a in the Treatment and Chemoresistance of GC

At present, the main method to treat GC is chemotherapy based on cisplatin (DDP), but it is prone to cause drug resistance problems. Recent studies have found that miR-34a is associated with drug resistance of DDP.[75] Reinforced miR-34a enhanced the sensitivity of GC cells to DDP. Further investigation demonstrated that miR-34a regulated the proliferation and apoptosis of cancer cells by targeting MET, thus regulated the sensitivity of GC cells to DDP. Moreover, studies have shown that lncRNA HOTAIR is associated with DDP resistance in GC. The weakened expression of lncRNA HOTAIR up-regulated miR-34a and inhibited the PI3K/AKT and WNT/β-catenin signaling pathways, thereby inhibiting DDP resistance in GC.[19] In addition, Jang et al[76] developed a nanoscale stable gene delivery system to enhance the delivery efficiency of miR-34a in vivo by encapsulating the poly-L-lysine-graft-imidazole (PLI)/miR-34a complex in the PEGylation (polyethylene glycol) liposome vehicles. The increased miR-34a not only enhanced its negative regulation on target genes, thereby inhibiting the occurrence, development, migration, and invasion of tumors, but also restored drug sensitivity. Moreover, miR-34a enhanced the sensitivity of GC cells to luteolin by directly targeting hexokinase 1 (HK1).[52] Luteolin exerts anti-tumor effects by inhibiting cell proliferation, promoting apoptosis, and inhibiting cancer cell metastasis and angiogenesis.[77,78] miR-34a was down-regulated in luteolin-resistant GC cells. When miR-34a was up-regulated, the chemosensitivity of drug-resistant GC cells to luteolin was

improved. Further investigation revealed that there was a binding-site of miR-34a in the 3′-UTR of HK1, which is the first restriction enzyme functioned in glycolysis.[79,80] miR-34a reprograms metabolic processes by targeting HK1 to increase the chemosensitivity of GC cells to luteolin. Suzuki et al also presented evidences to demonstrate that miR-34a inhibited the proliferation, migration, and invasion of gastrointestinal stromal tumor cells by targeting PDGFRA.[81] Therefore, exogenously increasing miR-34a may attenuate chemoresistance and improve the therapeutic effect of GC.

miR-34a in CRC

CRC is the third most common malignant tumor, with a high incidence of more than a million new cases diagnosed every year in the world.[82–84] CRC has an especially high mortality rate in China, mainly due to cancer invasion and metastasis.[85] Studies have demonstrated that miR-34a is closely related to the proliferation, differentiation, migration, treatment, and prognosis of CRC.

miR-34a Expression in CRC

Abnormal expression of miR-34a has been identified in CRC. Several studies have shown that miR-34a is highly expressed in patients with CRC. For instance, miR-34a was measured in tumors and adjacent noncancerous tissues from 159 American and 113 Chinese colon cancer patients using qPCR method. The results showed that miR-34a expression was up-regulated in two different ethnic CRC patients, and there was no significant correlation between miR-34a expression and TNM staging.[86] Wang et al also reported that miR-34a was highly expressed in CRC tissues, and miR-34a expression was correlated with TNM staging.[87] Moreover, the results obtained from the GEO database (accession numbers: GSE28364 and GSE83924) showed that the expression of miR-34a was significantly increased in the adenoma and cancer tissues as compared with the normal tissues.[88,89] However, several studies have identified that miR-34a is under-expressed in CRC tissues and is closely related to the progression of CRC.[90–94] In addition, a recent study found that a polymorphism rs35301225 in miR-34a was associated with tumor size, tumor differentiation and metastasis in Chinese CRC patients.[95] Jun et al investigated the relationship between the methylation status of miR-34 gene and the expression of miR-34a in paired CRC tumor and normal tissues. The results showed that the methylation level of miR-34a in tumor tissues was significantly higher than that in normal tissues ($P = 0.012$), indicating that the methylation of miR-34 gene is related to the pathogenesis of CRC.[96] These studies have shown that the expression of miR-34a is indeed closely related to CRC.

The Role of miR-34a in the Proliferation and Differentiation of CRC

Studies have demonstrated close relationship between miR-34a and the proliferation and differentiation of CRC. Formin-like 2 (FMNL2), a member of the family of homogenic proteins, is a catalyst for linear actin polymerization and is involved in many basic actin-dependent processes, including cell differentiation, proliferation, and cytokinesis.[97,98] E2F transcription factor 5 (E2F5) is an important member of the E2F-family transcription factors, and plays a crucial role in the regulation of the cell cycle, especially in early G1 events, including G0/G1 transition.[99] miR-34a inhibited proliferation and induced cell cycle arrest and apoptosis of CRC cells by targeting FMNL2 and E2F5.[100] In addition, miR-34a also inhibited the proliferation of CRC cells by binding to the 3′-UTR of high mobility group box 1 (HMGB1).[101] HMGB1 is a chromatin protein which can organizes the DNA and regulates transcription. Since HMGB1 is highly expressed and miR-34a is down-expressed in CRC, the binding ability of miR-34a with HMGB1 is weakened, which contributes to the proliferation and differentiation of CRC. In addition, miR-34a also affected the proliferation and differentiation of colon cancer cells by targeting CDK4, CDK6, CCNE2, E2F3, BCL2 and the other genes closely related to cell cycle and anti-apoptosis.[20] These findings suggest that miR-34a plays an important role in the proliferation and differentiation of CRC.

The Role of miR-34a in the Migration and Invasion of CRC

It has been shown that the interleukin 6 receptor (IL-6R)/signal transducer and activator of transcription 3 (STAT3)/miR-34a loop promoted EMT-mediated CRC migration and invasion.[102] Interleukin-6 (IL-6) is an important proinflammatory cytokine that can be produced by tumor cells. Elevated IL-6 level was closely associated with advanced tumors, tumor size, and tumor metastasis.[103,104] IL-6 exerts a biological effect by binding to its receptor IL-6R, resulting in activation of the carcinogenic transcription factor STAT3 and consequent inhibition of miR-34a. Low-expression of miR-34a reduced its binding ability to IL-6R and further activated STAT3. Thus, the activated IL-6R/STAT3/miR-34a loop was required for EMT, migration, and invasion of

CRC cells. Additionally, activation of the transcription factor p53 inhibited the expression of IL-6R and the activation of STAT3, resulting in increased expression of miR-34a and disruption of the homeostasis of the IL-6R/STAT3/miR-34a loop, thereby interfering with IL-6-induced migration and invasion, and preventing EMT-mediated metastasis and invasion of CRC.[105,106] miR-34a also inhibited CRC metastasis by regulating Notch signaling pathway.[107] It has been found that miR-34a inhibited the expression of notch homolog 1 (Notch1) and ligand of Notch1 (JAG1) by directly binding to their 3′-UTRs, thus promoting EMT, invasion, and migration of cancer cells.[108–110] Meanwhile, the downregulation of Notch1 and JAG1 decreased the expression of vimentin and fibronectin, and consequently weakened the migration and invasion of CRC cells. Lai et al observed that miR-34a inhibited the migration and invasion of CRC cells by regulating the SIRT1/p53 pathway.[111] Studies have demonstrated that miR-34a participates in EMT through transcription factors and p53 signaling pathways. For instance, activation of p53 induced miR-34a expression and downregulated zinc finger transcription factor 1 (Snail1) and zing finger e box-binding homeobox 1 (ZEB1), which consequently inhibited the migration and invasion of CRC cells. While Snail1 and ZEB1 bond to the e-box in the miR-34a promoter, resulting in inhibition of miR-34a and forming a double negative feedback loop to regulate EMT. In addition to inhibiting Snail1, miR-34a also negatively regulated Slug, ZEB1, zinc finger protein 281 (ZNF281), etc., thereby stabilizing the epithelial phenotype.[112–114] Additionally, several studies have shown that lncRNAs promote metastasis and invasion of CRC cells through competitively binding to miR-34a and activation of Wnt/β-catenin signaling pathway, such as HNF1A-AS1, GAPLINC, NEAT1, and XIST.[115–118] These findings indicate that different molecular mechanisms were involved in the miR-34a-mediated inhibition of invasion and migration of CRC.

The Role of miR-34a in the Diagnosis and Prognosis of CRC

Aberrant miRNAs including miR-34a have been identified as potential prognostic biomarkers of CRC.[119,120] In CRC, low-expression of miR-34a was reversely correlated with the expression of proto-oncogene c-Met, Snail1, and β-catenin, which were closely related to the distant metastasis of CRC. Multivariate COX regression analysis revealed that miR-34a expression was an independent prognostic factor for CRC recurrence. Furthermore, clinical data showed that miR-34a methylation was detected in 45.1% of 94 primary CRCs and was associated with liver metastasis and lymph node metastasis. Wu et al further confirmed that there was a close relationship between methylation of miR-34a and lymph node metastasis in CRC patients.[121] These results indicate that miR-34a may be considered as a potential biomarker for the prognostic of CRC.

The Role of miR-34a in the Treatment and Chemoresistance of CRC

In recent years, many studies have found that miR-34a participated in chemotherapeutic drug-resistance of CRC. For instance, miR-34a induced the resistance of CRC cells to oxaliplatin by inhibiting macrophage autophagy via transforming growth factor-β (TGF-β)/drosophila mothers against decapentaplegic 4 (Smad4) pathway.[122] miR-34a increased the sensitivity of CRC cells to 5-fluorouracil (5-FU) by inhibiting the expression and activity of lactate dehydrogenase A (LDHA), indicating that miR-34a-mediated inhibition of glucose metabolism may be a therapeutic target for patients with chemotherapy-resistant colon cancer.[123] Moreover, a natural compound resveratrol increased the expression of miR-34a in cancer cells and down-regulated the target genes E2F3 and SIRT1, thus inhibiting the growth of cancer cells.[124] Therefore, resveratrol exerted significant anti-tumor effects. It has been reported that Notch1 and Notch homolog 2 (Notch2) participate in various biological processes such as cell apoptosis and proliferation, and BCL2 is involved in cell apoptosis. *Spica prunellae* increased the level of miR-34a and enhanced its binding ability with target genes Notch1, Notch2, and BCL2, thereby inhibiting the growth of CRC cells.[125] Curcumin difluoride (CDF), a new dietary ingredient curcumin analog, significantly inhibits cell growth and induces apoptosis in cancer cells resistant to 5-fluorouracil and oxaliplatin. The mechanistic study showed that CDF restored the expression of miR-34a in CRC cells by removing the methylation of miR-34a promoter.[94] In addition, studies have revealed that lncRNA KCNQ1OT1 enhances the chemical metabolism of oxaliplatin in CRC by targeting the miR-34a/autophagy related 4B cysteine peptidase (ATG4B) pathway.[126] Immunotherapy is a promising method for treating tumors in recent years, but it is prone to inducing tumor immune rejection. At present, several studies have shown that miR-34a affects the expression of the interferon stimulating genes in tumor microenvironment. Koelzer et al found that activation of E2F1 was an adverse event during dendritic cell (DC) maturation. miR-34a-mediated down-regulation of E2F1 and consequent death associated protein kinase 2 (DAPK2)

and Sp1 transcription factor (Sp1) led to immaturity of DCs, therefore suppressing the immune response.[127]

miR-34a in HCC

HCC is the fifth most common malignancy in the world and the second leading cause of cancer-related deaths worldwide.[128,129] In China, the incidence of HCC appears to be increasing every year, and the mortality rate ranks at the third in GICs. Recent studies have demonstrated that miR-34a is closely related to the proliferation, differentiation, migration, treatment, and prognosis of HCC.

miR-34a Expression in HCC

miR-34a has been identified to be abnormally expressed in HCC. For instance, Sun et al detected the expression of miR-34a in 60 HCC tissues, and found that miR-34a was lowly expressed in tumor tissues as compared with normal tissues.[130] The expression of miR-34a in HCC tissues was related to clinical stage and lymph node metastasis. This is consistent with a recent study that the expression of miR-34a was sequentially reduced in normal tissues, liver cirrhosis (LC) tissues, and HCC tissues.[131] Moreover, Xie et al confirmed that miR-34a was down-regulated in HCC tissues, and the proportion of methylation in the promoter region of miR-34a was higher in tumor tissues than that in non-tumor tissues.[132] However, no correlation between the methylation and expression of miR-34a and the clinicopathological features of patients was observed. Fang et al analyzed the expression of miR-34a in GEO datasets (accession numbers: GSE10694, GSE22058, GSE21362, GSE67882) and found that miR-34a was downregulated in HCC tissues with no heterogeneity.[133] These findings indicate that down-expression of miR-34a is involved in the progression of HCC.

The Role of miR-34a in the Proliferation of HCC

It has been found that miR-34a suppressed the proliferation and induced apoptosis of HCC cells by regulating the expression of histone deacetylase 1 (HDAC1).[130] miR-34a inhibited HDAC1 expression by directly binding to its 3′-UTR. Inhibition of HDAC1 restored its target genes by inducing histone and non-histone deacetylation.[134] Down-regulated miR-34a led to over-expression of HDAC1 and silence of some key genes that regulate cell cycle and apoptosis, thereby promoting the proliferation and inhibiting the apoptosis of cancer cells. In addition, miR-34a regulated the telomerase activity in human HCC by targeting the forkhead box protein M1 (FoxM1)/c-Myc pathway, thereby inducing cell senescence and involving in the development of HCC.[135] Another study demonstrated that the expression level of miR-34a was negatively correlated with telomerase index including telomere length and telomerase activity. miR-34a inhibited telomerase activity and telomere length in HCC cells, resulting in senescence-like phenotype and influence of cell survival. Both FoxM1 and c-Myc are involved in the activation of telomerase reverse transcriptase (hTERT) transcription and avoiding cell senescence.[136,137] Therefore, miR-34a played an anti-tumor role by regulating the telomeres pathway in the senescence process of cells. Moreover, Jiang et al investigated the relationship between the risk of HCC and a polymorphism rs1057317 in the binding-site of miR-34a in the Toll-like receptor 4 (TLR4) gene.[138] They found that rs1057317 was significantly associated with the risk of developing HCC, suggesting that the miR-34a/TLR4 axis plays an important role in the development of HCC. In addition, lncRNAs were observed to regulate the expression of miR-34a and to participate in the process of HCC. For instance, lncRNA CCAT2 promoted the growth of HCC tumors through a positive feedback loop of CCAT2-miR-34a-FOXM1.[139] These studies have shown that miR-34a is closely related to the proliferation of HCC.

The Role of miR-34a in the Migration and Invasion of HCC

Many studies have examined the roles of miR-34a in the migration and invasion of HCC. It has been found that the expression level of miR-34a in the metastatic/invasive HCC tumor tissues is lower than that in the non-invasive HCC tumor tissues, suggesting that miR-34a is associated with the migration and invasion of HCC cells. Further investigation showed that miR-34a inhibited the migration and invasion of HCC by down-regulating c-Met.[140] c-Met is a hepatocyte growth factor (HGF) receptor that activates MAPK pathway by binding to HGF, leading to constitutive activation of downstream components of the MAPK pathway, thereby inducing the migration and invasion of cancer cells.[141–143] Moreover, miR-34a affected the non-glutamate decomposition of glutaminase 2 (GLS2) through the Dicer-miR-34a-Snail1 pathway, which promotes miR-34a maturation by interacting with Dicer and stabilizing Dicer.[144] Up-regulated miR-34a inhibited EMT by suppressing Snail1 expression, ultimately inhibiting the migration and invasion of HCC. LncRNA-MUF, acting as the competitive endogenous RNA of miR-34a, restored Snail1 and promoted EMT, thus participated in the metastasis and

invasion of HCC.[145] These findings indicate that miR-34a influences the migration and invasion of HCC through different regulatory mechanisms.

The Role of miR-34a in the Diagnosis and Prognosis of HCC

Currently, several studies have shown the diagnosis and prognostic value of miR-34a expression in HCC patients.[146,147] The low-expression of miR-34a was associated with vascular invasion and advanced TNM stage.[146] Meanwhile, Kaplan-Meier analysis revealed that decreased miR-34a expression was associated with poor overall survival of HCC patients. Multivariate analysis showed that miR-34a expression was an independent prognostic factor for HCC.[146] Additionally, Xiang et al showed that low-expression of miR-34a in serum and intratumoral tissues was an independent risk factor for bone metastasis in HCC patients.[147] These findings suggest that miR-34a might be used as an indicator of diagnosis and prognosis of HCC.

The Role of miR-34a in the Treatment of HCC

Sorafenib, a multi-kinase inhibitor, is a first-line targeted chemotherapy for HCC. Sorafenib induces cell apoptosis by upregulating p53 pro-apoptotic effector p53 upregulated modulator of apoptosis (PUMA) and BCL2-associated X protein (Bax) and inhibiting anti-apoptotic BCL2 in tumor cells, thereby exerting antitumor effects. It has been reported that miR-34a influenced the therapeutic efficacy of sorafenib in HCC.[148] Low-expression of miR-34a was significantly negatively correlated with high-expression of BCL2 in HCC tissues. Bioinformatics and dual luciferase reporter assays have shown that miR-34a inhibited BCL2 expression by directly binding to its 3′-UTR. Therefore, miR-34a enhanced sorafenib-induced apoptosis of cancer cells by repressing the expression of BCL2. Moreover, a strong synergistic interaction between miR-34a and erlotinib, a tyrosine kinase inhibitor, was observed in the treatment of HCC.[149] These findings provide new clinical strategies for the treatment of HCC.

miR-34a in PC

PC is a highly malignant tumor, which is difficult to be diagnosed and treated. About 90% of PCs are ductal adenocarcinomas originating from the ductal epithelium, named pancreatic ductal adenocarcinoma (PDAC). The morbidity and mortality of PC have significantly increased in recent years and have become the leading cause of cancer-related deaths.[150] PC has the characteristics of hardly early diagnosis, low cure rate, and poor prognosis.[151,152] At present, many studies have examined the relationship between miR-34a and PC.

miR-34a Expression in PC

It has been reported that the expression levels of miR-34a in plasma and tissues of patients with PDAC were significantly lower than those of benign pancreatic lesions and healthy subjects.[153] The levels of miR-34a were also significantly associated with the clinicopathological features including tumor size, TNM stage, invasion, overall survival, and lymph node metastasis. Sun et al reported that miR-34a was down-regulated in PDAC tissues compared with normal tissues and was decreased along with TNM staging.[154] Meanwhile, the expression level of miR-34a was closely related to the prognosis of patients with PDAC. However, miR-34a was found to be up-regulated in the serum of patients with PDAC.[155] The results obtained from the GEO database (accession numbers: GSE32688 and GSE15471) also indicated that miR-34a expression in PC was up-regulated.[156,157]

The Role of miR-34a in the Proliferation of PC

Several studied have explored the relationship between miR-34a and the proliferation of PC cells. Kent et al found that reinforced miR-34a in two PDAC cell lines significantly inhibited the proliferation of cancer cells.[158] Moreover, the expression levels of endogenous miR-34a in various PDAC cell lines were low or even absent, suggesting a negative relationship between miR-34a and proliferation of PC cells. In addition, studies have reported that miR-34a played a key role in the growth and apoptosis of PC cells, mainly through the regulation of Notch-1 signaling pathway, which is closely related to the cell growth and apoptosis.[159] miR-34a also inhibited the proliferation of cancer cells by binding to lncRNAs.[154] The lncRNA X inactive specific transcript (XIST) plays an important role in the development of PC, and promotes the proliferation, migration and invasion of cancer cells. Interestingly, miR-34a is down-regulated and XIST is up-regulated in PC cells. miR-34a is a target gene of XIST, and is negatively correlated with XIST expression, suggesting a crucial role of miR-34a in the proliferation of PC.[154] miR-34a also participated in PC cell proliferation by targeting CD44 and CDK6.[20] These results confirm that miR-34a plays a crucial role in the proliferation of PC.

The Role of miR-34a in the Migration and Invasion of PC

EMT is very important for the migration of cancer cells. Studies have revealed that absence of miR-34a led to migration, invasion, and anti-apoptosis of PC cells.[160] Further investigation demonstrated that miR-34a inhibited tumor migration and invasion by repressing the expression of Snail1, a target gene of miR-34a. Snail1 gene products a zinc finger protein, which promotes EMT by inducing the transcription of mesenchymal genes (such as N-cadherin) and inhibiting the transcription of epithelial genes (such as E-cadherin), thereby resulting in migration and invasion of cancer cells.[161,162] Overexpression of miR-34a suppressed the expression of Snail1, which in turn up-regulated E-cadherin. Moreover, the HDAC inhibitor Vorinostat (SAHA) inhibited the expression of EMT inducers Zeb-1, Snail, and Slug by up-regulating the expression of miR-34a, thereby attenuating the migration and invasion of PC cells.[163] These results illustrated key roles of miR-34a in the migration and invasion of PC cells.

The Role of miR-34a in the Diagnosis and Prognosis of PC

It was found that the expression level of miR-34a was significantly associated with tumor size, TNM stage, invasion, overall survival, and lymph node metastasis of PC.[153] Alemar et al determined the expression of miR-34a in the tissues of normal pancreas, chronic pancreatitis, and PDAC. The results showed that the expression level of miR-34a was closely related to the clinicopathological features of patients, suggesting that miR-34a may be used as a biomarker for the diagnosis and prognosis of PDAC.[155] Furthermore, CpG methylation of miR-34a was also employed as a diagnostic indicator for the prognosis of patients with PC.[164] Akamatsu et al[165] found that the expression level of miR-34a in serum could be used as a biomarker to distinguish between PDAC and autoimmune pancreatitis (AIP). These studies indicate that miR-34a and its methylation levels may be used as indicators for diagnosis and prognosis in patients with PC.

The Role of miR-34a in the Treatment of PC

A recent study on the relationship between miR-34a and the treatment of PC showed that lipid-based nanoparticles encapsulating miR-34a exhibited anti-tumor effects on PC.[166] Moreover, Feng et al found that simultaneous overexpression of miR-34a and miR-126 had strong anti-tumor effects in PC.[167] In addition to using miRNAs to enhance anti-tumor effects, another study reported that the combination of miR-34a and polo like kinase 1 (PLK1) siRNA delivered by biodegradable amphiphilic polyglutamate amine polymer nanocarrier (APA) markedly enhanced anti-tumor effects of miR-34a in the treatment of PC.[168] These studies demonstrated potential clinical applications of miR-34a in the treatment of PC.

miR-34a in GBC

GBC is one of the most common malignant gastrointestinal tumors in the world, accounting for 80–95% of global biliary carcinoma, and is also the main cause of global biliary malignant tumor-related death.[169–171] GBC is a highly aggressive and fatal disease whose incidence is closely related to geography, race, and gender.[170,172] Because of the lack of specific symptoms of GBC or reliable sensitive markers, it is difficult to diagnose GBC at an early stage, resulting in low survival rate. It has been reported that miR-34a is down-regulated in GBC,[173] but few studies focus on the relationship between miR-34a and the prognosis of GBC.

Jin et al measured miR-34a expression and telomere length in 77 gallbladder adenocarcinomas and 36 non-tumor tissues.[173] They found that miR-34a expression was significantly decreased in GBC tissues with long telomere length and poor survival rates and prognosis of GBC patients. Forced miR-34a expression attenuated the colony forming ability of $CD44^{+}$ $CD133^{+}$ GBC stem cell-like cells in vitro and inhibited the growth of xenograft tumors in vivo, indicating that miR-34a acted as a tumor suppressor in GBC. Simultaneously, the relationship between miR-34a and telomere length was further studied, and it was found that miR-34a reduced telomere length by down-regulating the expression of protein phosphatase 1 regulatory subunit 10 (PNUTS). PNUTS mediates the regulation of chromatin structure during cell transition from mitosis to interphase. Therefore, highly expressed miR-34a shortened the length of telomerase and inhibited the development of GBC by inhibiting the expression of PNUTS. These findings suggest that low-expression of miR-34a and long telomere length may be used as biomarkers of poor prognosis in patients with GBC and that miR-34a gene is a potential target for the treatment of GBC.

Summary

miR-34a is dysregulated in GICs with consistent low-expression in EC, GC, HCC, and GBC, but contradictory expression in CRC and PC, demonstrating complex regulatory roles of miR-34a in GICs. Numerous studies have revealed that miR-34a plays a critical role in the proliferation,

anti-apoptosis, cell cycle arrest, migration, invasion, and treatment of GIC cells, through targeting a number of oncogenes, such as BCL2, CCND1, CCNE2, CD44, CDK4, CDK6, E2F1, E2F3, E2F5, FOXM1, MET, MMP2, MMP9, MYC, NOTCH1, SIRT1, SNAIL1, STAT3, etc. These indicate that miR-34a exerts important roles in the development, metastasis, and prognosis of GIC patients via signal pathways including MAPK/Ras, Wnt/β-Catenin, and PI3K/Akt. Thus, researchers have proposed augmenting miR-34a expression as a candidate therapeutic strategy and developed a liposome-capsuled miR-34a mimic (MRX34) for treating cancer patients in clinic.[20,174-176] Although acceptable anti-tumor activity in patients was achieved, the clinical trial was terminated because of severe immune-related adverse effects. Hence more studies on the immune-regulatory role of miR-34a in GICs are still needed to be further elucidated. Even though, due to the potent tumor-suppressive roles of miR-34a in GICs, new strategies with elimination of miR-34a-mediated immune-related adverse events might be beneficial to cancer therapy, for instance, formulation of miR-34a with antibody or nanoparticle for improving the targeting activity, decreasing the dosage, or combination with other anti-cancer drugs. This review systematically outlined the regulatory activities of miR-34a in GICs and provided evidences to support miR-34a as a promising target for cancer therapy.

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Disclosure

The authors report no conflicts of interest in this work.

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