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MINIREVIEWS

Role of microRNA-7 in digestive system malignancy

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Abstract

There are several malignancies of the digestive system (including gastric, pancreatic and colorectal cancers, and hepatocellular carcinoma), which are the most common types of cancer and a major cause of death worldwide. MicroRNA (miR)-7 is abundant in the pancreas, playing an important role in pancreatic development and endocrine function. Expression of miR-7 is downregulated in digestive system malignancies compared with normal tissue. Although there are contrasting results for miR-7 expression, almost all research reveals that miR-7 is a tumor suppressor, by targeting various genes in specific pathways. Moreover, miR-7 can target different genes simultaneously in different malignancies of the digestive system. By acting on many cytokines, miR-7 is also involved in many gastrointestinal inflammatory diseases as a significant carcinogenic factor. Consequently, miR-7 might be a biomarker or therapeutic target gene in digestive system malignancies.

Key words: MicroRNA-7; Digestive system malignancy; Tumor biomarker; Target gene; Inflammation

Core tip: MicroRNA (miR)-7 targets different genes in various complicated pathways and plays diagnostic, prognostic, anti-metastatic, and therapeutic roles in digestive system malignancies. MiR-7 might be a biomarker or therapeutic target gene in digestive system malignancies, even in the precancerous lesions (inflammatory disease).

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INTRODUCTION

MicroRNAs are small noncoding RNAs consisting of 18-25 nucleotides that post-transcriptionally regulate expression of target genes, and are involved in cell proliferation, epithelial-mesenchymal transition (EMT), apoptosis, migration, invasion and metastasis[1-3]. miRNAs have emerged as potential critical regulators of carcinogenesis and tumor progression[4,5].

The digestive system is composed of many ducts and glands, and because of its complicated physiology and anatomy, numerous diseases may occur, especially malignancies including the third, fourth and eighth most common cancers worldwide: Colorectal cancer (CRC), gastric cancer (GC) and esophageal cancer, respectively[6,7], as wells as the leading cause of cancer-related death: Pancreatic cancer (PC)[8]. According to the 2014 cancer statistics, the combined cancer mortality rates have been continuously declining for the past two decades. However, the incidence of some digestive system malignancies, including cancers of the esophagus, liver, anus and pancreas, is increasing. Moreover, with rising death rates for cancers of the liver, anus and pancreas, and other non-digestive cancers, cancer is still the second leading cause of death following heart disease[8]. Therefore, it is necessary for us to explore novel molecular mechanisms, and screen for the most effective therapeutic methods to avoid the majority of patients succumbing to these digestive malignancies.

MicroRNA (miR)-7 is an evolutionarily conserved miRNA that is involved in the development of the eye and pancreas in Drosophila. Li *et al*[9] reported that miR-7 is repressed by the transcription factor Yan, which is degraded while mediating epidermal growth factor receptor (EGFR) signaling. Also, miR-7 is expressed abundantly in human pancreas and endocrine cells and has a specific role in endocrine cell differentiation and function[10]. It has been demonstrated that miR-7 is a tumor suppressor in breast, lung and ovarian cancers, and glioblastoma, mainly focusing on its relationship with EGFR[11-15]. Accumulating evidence shows that miR-7 can simultaneously target a variety of mRNAs involved in diverse signaling pathways in different tumors. However, no specific review has described the role of miR-7 in digestive tract malignancies. In this review, we focus on current research on miR-7 in order to elucidate its role in digestive system malignancies or their precancerous lesions, with reference to its expression, signaling pathways, and role as a circulatory biomarker.

EXPRESSION OF MIR-7

By comparing the differential expression of miRNAs in pancreatic islets (endocrine) and acinar (exocrine) tissue in rats, using microarray and quantitative polymerase chain reaction (qPCR), Bravo-Egana *et al*[16] revealed that miR-7 was ranked highest among the 17 miRNAs preferentially expressed in islets, suggesting that it acts as an endocrine miRNA. Another two studies reported that miR-7 was expressed at a high level during human pancreatic islet development[10,17]. For malignancy, it has been demonstrated that miR-7 is downregulated in cancer tissue of digestive malignancies such as GC[18-20], CRC[21,22] and hepatocellular carcinoma (HCC)[23] by comparison with normal tissues, suggesting that it acts as a suppressor. A similar conclusion was drawn in a study of hydroxycamptothecin-resistant GC cells[24]. In some inflammatory diseases, such as gastritis and Crohn's disease[25], the level of miR-7 is also lower than that in normal tissue, which suggests that it is an inflammation-related miRNA participating in the process of digestive cancer.

In contrast, using the same method, Suto *et al*[26] discovered that miR-7 level was higher in CRC tissue than in adjacent normal tissue, induced by EGFR mutations. However, it was found that the aforementioned results would be opposite when the EGFR protein expression was positive in CRC. Finally, they concluded that low miR-7 expression resulted in poorer prognosis than high expression. Ahmed *et al*[27] identified the expression of miR-7 in stool samples from 40 cases of colon cancer (TNM stages 1-4), and found that miR-7 was one of the 12 increased miRNAs, which they then recognized as a diagnostic gene. In HCC, Fang *et al*[28] speculated that owing to inactivation of the transcriptional regulators and/or failure to promote miR-7 expression, there is no alteration of its expression between tumor and adjacent normal tissues. However, miR-7 and miR-21 are overexpressed in esophageal squamous cell carcinoma (ESCC) and related to its differentiation[29].

From Table 1, we can speculate the reasons for the divergent views about the expression of miR-7 under different conditions, including[30]: (1) heterogeneity of different malignancies/diseases; (2) different study sample sizes; and (3) the standards were not the same (*e.g.,* whether or not to include patients with prior cytotoxic therapy). Based on the published studies, we conclude that miR-7 could be an oncogene or tumor suppressor in the digestive system depending on the specific gene targeted (Table 2).

GC

The pathogenesis of GC has been extensively studied, and there is a consensus that intestinal gastric carcinogenesis is a multistep process starting with chronic gastritis triggered by *Helicobacter pylori*, progressing through atrophy, intestinal metaplasia and dysplasia to carcinoma (Correa model)[31]. Thus, inflammation is a significant event in gastric carcinogenesis, whereas miR-7 is an inflammation-mediated miRNA inversely

Table 1 Expression of microRNA-7 in the digestive system

Cancer	Sample	Sap No.	Method	Exp	Role	Ref.
Colon	Stool	60	qPCR	↑	Diagnostic	[27]
CRC	Tissue	80	qPCR	↓	Diagnostic/therapeutic	[21]
CRC	Tissue	8	RT-PCR	↓	Therapeutic	[22]
CRC	Tissue	105	qRT-PCR	↑	Prognostic	[26]
ESCC	Tissue	34	Microarray/qRT-PCR	↑	Differentiation	[29]
GC	Tissue	40	ISH/IHC	↓	Inhibits metastasis/EMT	[18]
GC	Tissue	23	Microarray qRT-PCR	↓	Inhibits invasion/metastasis	[19]
GC	Tissue	28	RT-PCR	↓	Represses inflammation	[20]
HCC	Tissue	10	Microarray qRT-PCR	-	Therapeutic/diagnostic/prognostic	[28]
HCC	Tissue	12	qRT-PCR	↓	Tumor suppressor	[23]
HCC	Tissue	429	Chip assay	↓	Prognostic	[43]
CD	Tissue	-	RT-PCR	↓	Therapeutic	[25]

↓: MiR-7 is downregulated; ↑: MiR-7 is upregulated; −: There is no alteration for expression of miR-7, or no mention. Sap No.: Sample number; Exp: Expression; ISH/IHC: *In situ* hybridization/immunohistochemistry; CRC: Colorectal cancer; GC: Gastric cancer; HCC: Hepatocellular carcinoma; ESCC: Esophageal squamous cell carcinoma; EMT: Epithelial–mesenchymal transition; qPCR: Quantitative polymerase chain reaction.

Table 2 Function of microRNA-7 by targeting diverse genes

Cells	Function of miR-7	Target	Ref.
CCA	Reduces migration, invasion and metastasis	LAT1	[41]
CRC	Inhibits proliferation, invasion and metastasis, and induces G1 arrest	PAX6	[21]
CRC	Inhibits proliferation and induces apoptosis	XRCC2	[22]
CRC	Suppresses proliferation, induces G1 arrest, and induces apoptosis	YY1	[37]
GC	Suppresses invasion and metastasis	IGF1R	[18]
GC	Inhibits proliferation, invasion and metastasis	EGFR	[19]
HCC	Decreases invasion and migration	PIK3CD/mTOR/p70S6K	[28]
HCC	Suppresses colony formation and induces cell cycle arrest	CUL5	[23]

CCA: Cholangiocarcinoma; CRC: Colorectal cancer; GC: Gastric cancer; HCC: Hepatocellular carcinoma; miR-7: MicroRNA; XRCC2: X-ray repair complementing defective repair in Chinese hamster cells 2; IGF1R: Insulin-like growth factor 1 receptor; EGFR: Epidermal growth factor receptor; mTOR: Mammalian target of rapamycin; CUL5: Cullin 5.

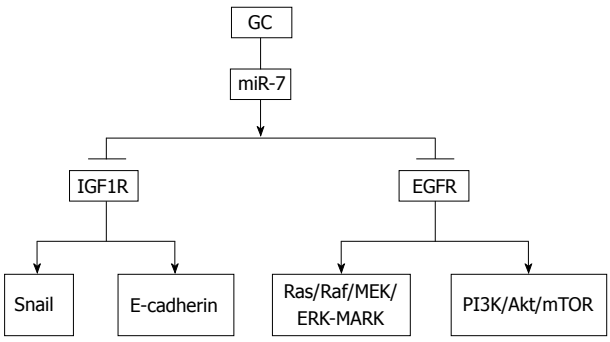

Figure 1 Pathway of microRNA-7 in gastric cancer. It has been revealed that miR-7 targets mainly IGF1R and EGFR. IGF1R: Insulin-like growth factor 1 receptor; EGFR: Epidermal growth factor receptor; GC: Gastric cancer; miR-7: MicroRNA-7; PI3K: Phosphoinositide 3-kinase; mTOR: Mammalian target of rapamycin.

correlated with many proinflammatory cytokines and inflammatory factors such as interleukin-1β and tumor necrosis factor-α. Three genes, *LPHN2*, *BASP1* and *MAFG*, targeted by miR-7 are induced in the cyclo-oxygenase (COX)-2/prostaglandin (PG) E2 pathways, which shows that miR-7 plays a significant part in gastric tumorigenesis with an inflammatory response[20].

MiR-7 suppresses GC cell invasion and metastasis both *in vitro* and *in vivo* by targeting the miR-7/insulin-like growth factor 1 receptor/Snail axis, which shows its EMT function and suggests that it can act as a therapeutic biomarker to prevent GC metastasis[18]. Xie *et al*[19] demonstrated that restoration of miR-7 significantly inhibited tumor cell viability, invasion and migration by suppressing EGFR expression. These results suggest that targeting miR-7 is a potential therapeutic option for GC (Figure 1).

PC

PC is one of the major leading causes of cancer mortality; the 5-year survival rate for pancreatic adenocarcinoma is < 5%, and most patients die within the first 2 years[8]. Therefore, there is an urgent need to explore novel therapeutic methods. In accordance with the expression of miR-7 in the pancreas, miR-7-3, which is one of the three endogenous genes potentially transcribed in the human genome, is upregulated by targeting mitogen-activated protein kinase (MAPK), suggesting that miR-7 is negatively modulated by an EGFR-MAPK feedback loop[32]. In an *in vitro* study, in

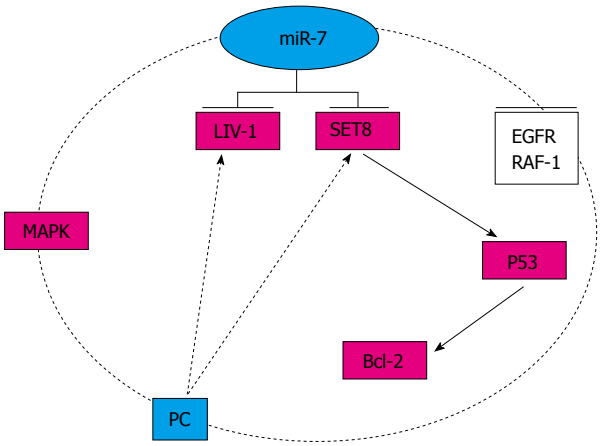

Figure 2 Pathway of microRNA-7 in pancreatic cancer. In PC, there is an EGFR-MAPK-miR-7 negative feedback loop, and LIV-1 and SET8 are two other targets. EGFR: Epidermal growth factor receptor; MAPK: Mitogen-activated protein kinase; PC: Pancreatic cancer; miR-7: MicroRNA-7; SET8: SET domain containing 8.

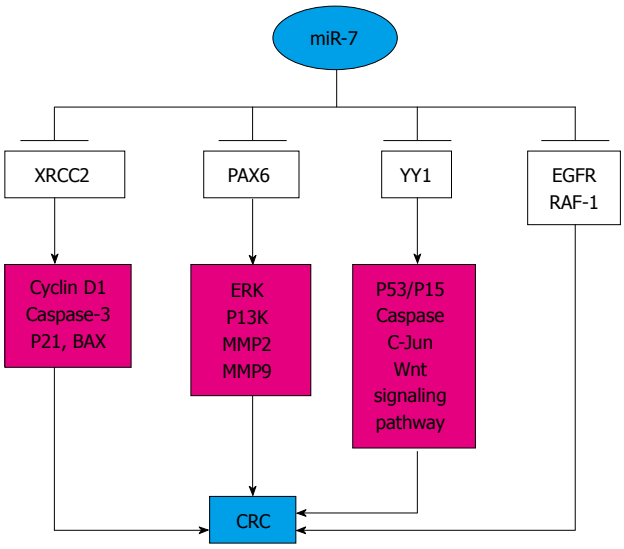

Figure 3 Pathway of microRNA-7 in colorectal cancer. MiR-7 can target various genes involving different pathways and act as a suppressor. CRC: Colorectal cancer; EGFR: Epidermal growth factor receptor; miR-7: MicroRNA-7. XRCC2: X-ray repair complementing defective repair in Chinese hamster cells 2; ERK: Extracellular signal-regulated kinase.

which miR-7 targeted SET domain containing 8 leading to increased p53 expression and decreased Bcl-2 level, curcumin suppressed cell growth, migration and invasion, and induced apoptosis in PC cells, indicating that targeting miR-7 is a useful therapeutic option for PC[33]. Although knockdown of LIV-1 (a zinc transporter) can upregulate expression of miR-7 in PC cells, the exact role of miR-7 in the maintenance of cancer-stem-cell-related phenotypes in PC remains unclear[34]. Future research will focus on identifying the exact pathway of miR-7 in PC, and only in this way, can research proceed from bench to bedside (Figure 2).

CRC

CRC is related to the mutation of genes such as P53, APC, SMAD4, PIK3CA, KRAS, ARID1A, SOX9 and FAM123B. Some minimal tailoring of therapy (selecting a chemotherapeutic agent based on toxicity, or not using anti-EGFR in those with KRAS-mutated tumors) can be offered to patients, however, the dream of truly individualized therapy remains elusive[35,36]. Based on the present studies, miR-7 can target specific genes to modulate the correlated pathways, and its decreased expression continuously participates in the process of CRC. MiR-7 is a tumor suppressor, which is mediated through the YY1-P53-Wnt signaling pathway, and plays pivotal roles in many cellular processes, such as development, differentiation, proliferation and apoptosis[37]. By targeting EGFR and *v-raf-1* murine leukemia viral oncogene homolog 1 (RAF-1), a low level of miR-7 suggests poor prognosis for CRC, and miR-7 precursor, alone or in combination with a monoclonal antibody, could be a novel therapy against CRC[26]. XRCC2 (X-ray repair complementing defective repair in Chinese hamster cells 2) participates in homologous recombination, and its relationship with miR-7 has been studied. *In vitro*, overexpression of miR-7 suppressed proliferation and induced apoptosis of CRC cells by directly targeting XRCC2 through decreasing cyclin D1 and increasing p21, caspase-3 and BAX expression[22]. In addition, the expression of paired box (PAX) 6 is inversely correlated with that of miR-7, and simultaneous activation of the extracellular signal-regulated kinase and phosphoinositide 3-kinase (PI3K) signaling pathways and regulation of the levels of matrix metalloproteinase (MMP) 2 and MMP9 could modulate the expression of PAX6 and miR-7 in opposing ways, which suggests that miR-7 is a promising therapeutic target for CRC[21]. Thus, further mechanisms mediated by miR-7 should be explored, which could be a promising approach for individually tailored therapy of CRC (Figure 3).

HCC

HCC, the third most common cause of cancer mortality worldwide, which develops from activation of cellular oncogenic pathways and abrogation of tumor suppressor pathways including the p53/p21^{WAF1} pathway, the p16^{INK4a}/CDK4/RB1/E2F pathway, the Wnt/β-catenin signaling pathway, transforming growth factor-α, c-myc, transcription factor NF-κB, insulin/IGF-I, and receptor tyrosine kinases and their downstream activators[38,39]. Several studies have shown that miR-7 participates in several pathways by targeting different genes in HCC. MiR-7 regulates the PI3K/Akt/mammalian target of rapamycin *in vitro* and *in vivo*, which functions downstream of EGFR, suggesting that miR-7 is a potential target for treating or diagnosing/prognosing HCC[28]. Likewise, ectopic expression of cullin 5, a novel target gene of miR-7, inhibits HCC cell proliferation, arrests cell cycle progression, and suppresses colony formation, although the exact pathway remains unclear[23]. Moreover,

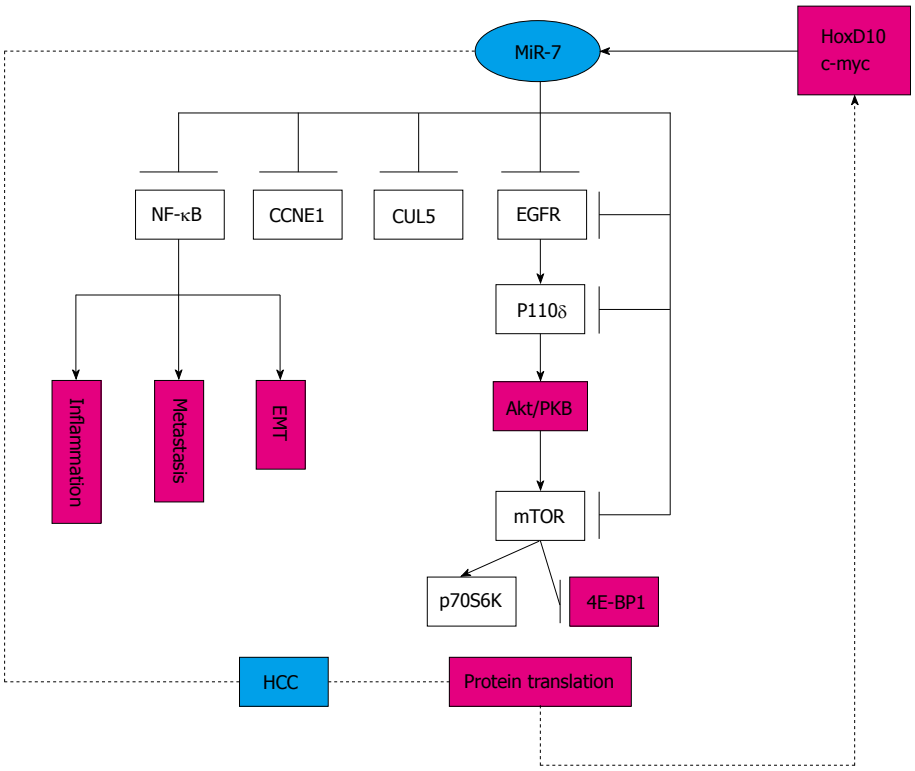

Figure 4 Pathway of miR-7 in hepatocellular carcinoma. MiR-7 can target various genes in the specific signaling pathway. HCC: Hepatocellular carcinoma; miR-7: MicroRNA-7; NF-κB: Nuclear factor κB; CCNE1: Cyclin E1; CUL5: Cullin 5; EGFR: Epidermal growth factor receptor; mTOR: Mammalian target of rapamycin; EMT: Epithelial–mesenchymal transition.

a member of the highly conserved cyclin family, CCNE1 (cyclin E1), is inversely correlated with miR-7 expression in HCC cell lines and clinical samples, indicating that it is a downstream mediator for miR-7, and miR-7 might be a candidate for the treatment of HCC[40]. Most studies in this field have been *in vitro* experiments, except one[28]. The detailed mechanisms remain to be elucidated, thus, the exact role of miR-7 in HCC needs further research (Figure 4).

OTHER DIGESTIVE MALIGNANCIES

MiR-7 also plays a role in other digestive tract malignancies such as cholangiocarcinoma and ESCC[29,41]. However, the expression and exact role of miR-7 in these two malignancies need to be verified.

INFLAMMATORY DISEASE

Inflammation makes a significant contribution to carcinogenesis and progression of malignancies[42]. In some conditions, inflammation such as chronic atrophic gastritis is defined as a precancerous lesion of GC. MiR-7 also participates in some inflammatory diseases, in addition to malignancies. The role of miR-7 in the progression from chronic inflammation to GC has been studied more thoroughly compared with other inflammatory diseases. Using established mouse models, Kong *et al*[20] have demonstrated that downregulation of miR-7 induced by PGE2 associated with inflammation, and activation of EGFR are critical steps in gastric carcinogenesis. Although the COX-2/mPGES-1/PGE2/EP2 pathway has been identified in gastric tumorigenesis, whether there is a similar mechanism mediated by miR-7 has not been established in other malignancies. It has been revealed that the expression of miR-7 is decreased in actively inflamed colonic tissues form patients with Crohn's disease, which is regulated by hCD98[25]. Similarly, chronic hepatitis has an important influence on HCC development, and hepatocyte nuclear factor 4α and NF-κB form a feedback circuit, for which miR-7 and miR-124 could be the targets[43]. These findings suggest that miR-7 is involved in many inflammatory diseases by activating many inflammatory/proinflammatory cytokines, and it will be intriguing to demonstrate the role of miR-7 in the regulation of alimentary inflammatory responses and carcinogenesis.

CIRCULATORY BIOMARKER

The diagnostic and prognostic biomarkers for some digestive malignancies including GC and CRC are still limited. Common circulatory markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 have inadequate sensitivity, therefore, exploring specific biomarkers is a significant breakthrough.

MiRNAs are stable in serum, plasma and body fluids (*e.g.*, stools and gastric juice), and their expression differs between tumor and non-tumor tissue. Some miRNAs, like miR-21, have been subjected to meta-

analysis and concluded to be diagnostic biomarkers for GC[44]. Wang *et al*[45] designed their study with three phases. In the discovery phase, they detected 723 miRNAs in 80 serum samples using microarrays; in the training phase they experimented on another 112 plasma samples using qPCR; and finally, they confirmed the results with 49 samples using a logistic model, and screened miR-7 as one of a panel that yielded high diagnostic accuracy to diagnose CRC. Compared with CEA, miR-7 has a higher receiver operating characteristic curve, sensitivity and specificity (0.897, 82% and 89%, respectively). Similarly, by analyzing the serum from 12 acute pancreatitis patients and three healthy controls, Liu *et al*[46] identified miR-7 as one of the three diagnostic and prognostic biomarkers. Although several systematic reviews[44,47-49] have investigated biomarkers for GC, none has shown that miR-7 could be a biomarker of GC.

CONCLUSION

Several studies have identified possible mechanisms mediated by miR-7 in specific malignancies of the digestive system, including some inflammatory diseases. No study has investigated miR-7 comprehensively, which may explain why different studies have discovered different targets for miR-7, or it may be because miRNA can form one-to-one, one-to-multiple or multiple-to-one relationships with its target genes[50]. Disruption of homeostasis in the digestive system is due to many pathways acting together in a complicated manner, which contributes to the progression from inflammatory diseases to malignancy. Furthermore, the genetic abnormalities in tumors are highly heterogeneous, and no two tumors are exactly alike, which raises a serious challenge. Consequently, more research should be conducted to verify whether miR-7 could be a biomarker or therapeutic target gene for digestive system malignancies.

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