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The role of microRNAs in cancers of the upper gastrointestinal tract

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Abstract

Cancers of the oesophagus, gastro-oesophageal junction and stomach (upper gastrointestinal tract cancers; UGICs) pose a major health risk around the world. Collectively, the 5-year survival rate has remained <15% and therapeutic improvements have been very slow and small. Therefore, novel molecules for early diagnosis, prognosis, prediction, and therapy are urgently needed. The role that microRNA (miRNA) molecules seem to play in UGICs are worth pursuing. miRNAs are small noncoding RNA molecules that regulate ~60% of coding genes in humans and, therefore, are pivotal in mediating and regulating many physiologic processes. miRNAs are deregulated in many disease states, particularly in cancer, making them important targets. Here, we review the building body of evidence regarding the alterations of miRNAs in UGICs. By suppressing translation and/or promoting degradation of mRNAs, miRNAs can contribute to carcinogenesis and progression of UGICs. In-depth studies of miRNAs in UGICs might yield novel insights and potential novel therapeutic strategies.

Introduction

Cancers of the upper gastrointestinal tract (UGICs) include those originating in the oesophagus, gastro-oesophageal junction and stomach. The incidence of adenocarcinoma involving the lower third of the oesophagus, gastro-oesophageal junction and proximal stomach has risen considerably in the past 30 years.[1] It is estimated that 38,780 new cases and 25,610 deaths are likely to occur in 2012 in the USA alone.[2] Gastric cancer is the fourth most common cancer and the second leading cause of cancer-related death in the world.[3] *Helicobacter pylori* infection, gastrin levels, germline mutations, dietary factors and other chronic gastric conditions are all factors involved in the development of gastric cancer. Our understanding of the molecular basis of carcinogenesis and progression of UGICs has lagged behind compared with many other tumour types. This knowledge deficit is creating a barrier in the development of effective therapeutics, and progress against UGICs has been unsatisfactory and slow. Consequently, outcomes for patients with UGICs have remained dismal, with 5-year survival rates <15%. Improved understanding of the role of microRNAs (miRNAs) in UGICs could lead to novel prevention strategies, early detection and improved therapeutics.

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Author contributions
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MicroRNAs

miRNAs are short (20–24 nucleotides) stable RNA molecules that are not translated into proteins but regulate 60% of coding genes by binding to mRNA molecules (to prevent their translation and/or promote degradation). More than 1,000 miRNAs have been identified, and they are involved in nearly all physiologic processes (as well as having a role in diseases like cancers). Novel functions and mechanisms by which miRNAs regulate genes are constantly being discovered.[4–6]

miRNA genes are located in intergenic regions but can also be in exonic or intronic regions of other genes.[7] In addition, miRNA genes can be found in the introns of protein-coding or non-protein-coding genes.[8] Each miRNA can target a large number of genes (mRNAs). In addition, each mRNA can be targeted by several miRNAs.[9] The many ways in which miRNAs engage mRNA have been described and new mechanisms are regularly being discovered.[8] Most commonly, miRNAs can either degrade an mRNA (when perfect complementarity is established) or inhibit its translation (when imperfect complementarity is established). The outcome is a reduction in the amount of a particular protein inside the cell.[4,10] In addition, some miRNAs can directly bind to the (open reading frame of the) DNA or modify the methylation status of a gene.[11] A mature miRNA can target mRNA binding proteins (functioning like a decoy).[12]

The genes that encode miRNAs are frequently located inside or close to fragile sites of chromosomes and are subject to considerable deregulation in cancer.[10] Alterations in the expression of miRNAs in cancer are related to deletions, mutations, polymorphisms, promoter hypermethylation and/or histone acetylation of miRNA genes as well as alterations in the miRNA processing machinery. Amplifications, translocations and/or transcript activations can also lead to changes in miRNAs.

Many miRNAs have been identified to act as oncogenes, tumor suppressors and important modulators in cellular pathways. The oncogenic or tumour suppressor function of miRNAs depends on the outcome of the target mRNA. Increased activity of oncomiRNAs leads to inhibition of tumour suppressor genes, facilitating cell proliferation and tumour progression. Decreased activity of tumour-suppressor miRNAs (tsmiRs) therefore leads to increased oncogene translation, contributing to tumour formation.[13] Certain miRNAs are involved in the regulation of metastasis (metastamiRs); these miRNAs can positively or negatively regulate cancer cell migration, invasion and metastasis.[14,15]

Some miRNAs are upregulated or downregulated in specific types of cancer (for miR-122 in hepatocellular carcinoma (refs: 1. Kota, J, Chivukula, RR, O'Donnell, KA, Wentzel, EA, Montgomery, CL, Hwang, HW, Chang, TC, Vivekanandan, P, Torbenson, M, Clark, KR, Mendell, JR, Mendell, JT. Therapeutic microRNA delivery suppresses tumorigenesis in a murine liver cancer model. Cell 2009;137(6): 1005–1017.http://www.ncbi.nlm.nih.gov/pubmed/19524505, Haussecker, D, Kay, MA. miR-122 continues to blaze the trail for microRNA therapeutics. Mol Ther 2010;18(2): 240–242.http://www.ncbi.nlm.nih.gov/pubmed/20125164,). Further research may yield tissue-specific miRs. This level of specificity could enable tumour-type-specific targeting. Some miRNAs are actively secreted in blood and other body fluids and could potentially be used for the early diagnosis of cancer and monitoring of therapy; circulating miRNAs have been described in UGICs.[16] Some miRNAs participate in genetic exchange among cells.[17] miRNA profiling can make a distinction between normal and malignant tissue[7] but, more importantly, since tumour-type-specific miRNA profiles (miRNomes) have been discovered, such observations lend themselves to establishing miRNomics as a diagnostic tool for uncovering the origin of tumours.[8] For example, miR-122 appears to be highly enriched in the liver, suggesting that

the discovery of more organ-specific miRNAs could improve our ability to target these processes.[18] For greater understanding of the mechanisms of deregulated miRNA, we recommend a previous report.[19]

miRNAs and oesophageal cancer

Microarray or real-time PCR and *in situ* hybridization have been used to determine and validate expression of miRNA in cell lines and tumour specimens. Many reports have described deregulated miRNA, their targets as well as their functions in the major oesophageal cancer histologic subtypes: oesophageal adenocarcinoma (Table 1) and oesophageal squamous cell carcinoma (Table 2).[20]

Oesophageal adenocarcinoma

OncomiRs—miRNA profiling and functional studies have been used to understand the mechanisms of progression of Barrett oesophagus to oesophageal adenocarcinoma. Several reports discuss the alterations in miRNAs in Barrett oesophagus and oesophageal adenocarcinoma and have identified targets and characterized their functional roles in the carcinogenesis of oesophageal adenocarcinoma. For example, miR-106b-25 polycistron is progressively upregulated in high-risk Barrett oesophagus to oesophageal adenocarcinoma; this upregulation is associated with genomic amplification and overexpression of *MCM7* locus at chromosome 7q22.1.[21] The upregulated polycistron targets and inhibits P21 and Bim proteins, which affect cell cycle and apoptosis, therefore contributing to oesophageal adenocarcinoma carcinogenesis.[21] Two independent reports have described upregulation of miR-196a in a progressive manner from Barrett oesophagus to Barrett oesophagus with dysplasia and finally to oesophageal adenocarcinoma; miR-196a targets *annexin A1 (ANXA1), small proline-rich protein 2C (SPRR2C)* and *S100A9*.[22,23] Expression of *programmed cell death receptor 4 (PDCD4)*, a tumour suppressor gene, decreased progressively and significantly with progression of Barrett oesophagus to oesophageal adenocarcinoma, but miR-21 expression was upregulated in high-grade dysplasia with Barrett oesophagus and oesophageal adenocarcinoma, consistent with *PDCD4* deregulation; functional studies have confirmed that miR-21 is a negative regulator of *PDCD4 in vivo* and play an oncogenic role in EAC.[25] Therefore, miR-21, miR-196a, and miR-192, which are upregulated in oesophageal adenocarcinoma but not in normal samples, and have been termed as oncomiRs.[27,28]

tsmiRs—Two miRNA alterations in Barrett oesophagus and oesophageal adenocarcinoma has been identified that might mediate progression to oesophageal adenocarcinoma: miR-31 showed frequent downregulation only in HGD and EAC cases suggesting association with transition from BM to HGD, while miR-375, showed marked downregulation exclusively in EACs and in none of the BM or HGD lesions, suggesting its association with progression to invasive carcinoma. it is, therefore, proposed that miR-31 and miR-375 might be specifically associated with early and late-stage malignant progression, respectively.[26] However, documenting the functional significance of such discoveries is difficult in this setting because of the lack of mature genetically engineered mouse models. Some of the work is, therefore, preliminary. For example, several studies have found alterations in miRNAs in Barrett oesophagus and oesophageal adenocarcinoma, but the target mRNAs have not been identified. miR-200 family members were downregulated in oesophageal adencarcinoma compared with Barrett oesophagus, and a significant inverse correlation was noted between miR-200 family expression and *zinc finger E-box binding homeobox 1 (ZEB1)* and *ZEB2* expression in Barrett oesophagus and oesophageal adenocarcinoma.[24] miR-203, miR-205, Let-7a/b/c, miR-345, miR-494, miR-193a and miR-375, are downregulated in oesophageal

adenocarcinoma and could be considered tsmiRNAs.[28–32] In-depth studies of these miRNAs will be important.

Osophageal squamous cell carcinoma

OncomiRs—A large number of miRNAs and their targets have been identified that are upregulated in oesophageal squamous cell carcinoma. These oncomiRs target important tumour suppressors. miR-21 has been reported by several independent groups to be an important oncomiR in oesophageal squamous cell carcinoma.[33–35] miR-21 targets *phosphatase and tensin homolog (PTEN)* and *PDCD4* and seems to promote progression of oesophageal squamous cell carcinoma; miR-21 should be explored as a therapeutic target for preclinical or clinical trials for subset of patients with high expression levels of this miRNA. Two reports note an upregulation of miR-25 and miR-92a in oesophageal squamous cell carcinoma, both of which target *CDH1*. This gene encodes E-cadherin, which is an important protein for maintaining normal epithelial phenotype—its downregulation can lead to epithelial–mesenchymal transition (EMT) and metastasis.[36,37] Both miRNAs promote migration and invasion through reduced expression of E-cadherin, and are associated with poor prognosis.[36,37] Upregulation of miR-10b has been reported in 95% of oesophageal squamous cell carcinomas, along with reduced expression of *KLF4* (*Krüppel-like factor 4*), an important tumour suppressor in the gastrointestinal tract.[38] *LATS2* (*large tumour suppressor homolog 2*) is a member of the *LATS* tumour suppressor family and is involved in Hippo signalling, which controls organ size and has a critical role in liver and gastrointestinal tract carcinogenesis. Frequent loss of heterozygosity of *LATS* has been reported in human oesophageal cancers, and miR-373 inhibits *LATS2 in vitro* and *in vivo*.[39] Therefore, miR-373 might have an oncogenic role worthy of further pursuit to gain therapeutic advantage.[39] Many more potential oncogenic miRNAs have been reported in oesophageal squamous cell carcinoma (Table 2, Figure 1).[20,22,40–46]

tsmiRs—Similarly, many downregulated miRNAs and their targets have been identified in oesophageal squamous cell carcinoma. Among these, miR-375 is the most promising tsmiR that is consistently downregulated either in tumour tissues or plasma from patients with oesophageal squamous cell carcinoma compared with healthy controls.[27,47–49] Hypermethylation of miR-375 promoter is the reported mechanism of its downregulation.[49] IGF1R and PDK1 are important components of IGF1 and the phosphatidylinositol 3-kinase (PI3K) pathways, which are frequently overexpressed in many malignancies and have a crucial role in promoting cell proliferation, survival and metastasis.[47] miR-375 could interact with the 3′-untranslated region of *IGF1R* and *PDK1* and downregulate their expression. Therefore, *IGF1R* and *PDK1* are two major targets of miR-375.[47,49] Another report suggests that miR-133a, a tumour suppressor, inhibits tumorigenesis and growth *in vivo* and inhibits *CD47*; overexpression of *CD47* correlates with poor prognosis.[50] miR-133a in concert with miR-145 and miR-133b target *FSCN1* (actin-binding oncogenic protein, Fascin homolog1) and thereby inhibit cell proliferation and invasion in oesophageal sqaumous cell carcinoma cells.[51] An *in vitro* study by Matsushima *et al*. demonstrated that the downregulation of miR-205 results in reduced cellular invasion and migration by targeting *ZEB2*; it also reduces EMT by decreasing E-cadherin expression.[52,53] Let-7a and miR-34a, reportedly involved in cancer stem cell regulation,[6] are downregulated in oesophageal squamous cell carcinoma.[54–56] Other tsmiRs in oesophageal squamous cell carcinoma include: miR-29c, which targets cyclin E without affecting cyclin dependent kinase (CDK) *CDK2* and *CDK6*;[57] miR-210, which targets *FGFRL1*,[58] and miR-223, which targets *ARTN*[59] (Table 2[52,53,55,60]).

miRNAs and gastric cancer

OncomiRs

Many overexpressed oncomiRs affect apoptosis and proliferation in gastric cancer. Overexpression of miR-181a in a gastric cancer cell line led to increased cell proliferation and inhibition of apoptosis by repression of tumour suppressor *KLF6*.[61] Several investigators have reported upregulation of miR-21 in gastric cancer (its targets, as mentioned above, are *PDCD4* and *PTEN*).[62–64] miR-196a/196b are markedly overexpressed in tumor tissues and serum of gastric cancer patients.[65,66] Increased miR-146a in gastric cancer directly targets SMAD4; and ectopic expression of miR-146a could improve proliferationis and inhibit apoptosis of gastric cancer cells.[67] Overexpression of miR-191 has been reported in the gastric cancer cell line MGC803 and in gastric cancer tissue; this miRNA regulates *NDST1* (*N-deacetylase/N-sulfotransferase 1)*.[68] Overexpression of miR-370 in gastric cancer tissue has been observed, leading to downregulation of *TGFBR2* (TGF-β type II receptor).[69] miR-126 overexpression leads to inhibition of *SOX2*, which seems to contribute gastric cancer carcinogenesis.[70] Thus it seems that many oncomiRs are worthy of pursuit and might become therapeutic targets in the future. More oncomiRNAs in gastric cancer are shown in Table 3 and Figure 2.[59,71–76]

tsmiRs

miR-181b and miR-182 were significantly downregulated in human gastric adenocarcinoma tissue samples compared to the adjacent normal gastric tissues. Functinally, overexpression of miR-181b suppressed the proliferation and colony formation rate of gastric cancer cells and decreased the expression of cAMP responsive element binding protein 1 (CREB1) by binding its 3′ untranslated region. Thereby, miR-181b and miR-182 may function as a tumor suppressor in gastric adenocarcinoma cells through negative regulation of *CREB1*.[77,78] miR-101 was downregulated in gastric cancer owing to microdeletions at miR-101 genomic loci that subsequently led to *EZH2* overexpression and *CDH1* dysfunction, especially in intestinal-type gastric cancer.[79] miR-124 inhibits gastric cancer cell proliferation by inducing cell cycle inhibitors P21 and P27 proteinsby targeting oncogenic *SPHK1*.[80] The miR-409-3p cluster also inhibits proliferation by targeting the transcriptional regulator *PHF10*.[81] *MYC*, an important modulator for cell growth and apoptosis, is downregulated by miR-429.[82] miR-296 is progressively lost during tumour progression and leading to aberrant overexpression of *SCRIB*[83] miR-375 is downregulated in gastric cancer and its targets are oncogenes *JAK2, PDK1* and *YWHAZ (14-3-3 zeta)*.[84,85] miR-486, reported as a tsmiR in gastric cancer by several investigators, negatively regulates the antiapoptotic glycoprotein OLFM4.[86] Let-7a, a tsmiRNA, has reduced expression in gastric cancer tissues and cell lines;[87–89] its target is *RAB40C*. miR-137 is a negative regulator of *CDC42* and is downregulated in gastric cancer as a result of hypermethylation.[90] Quantitative PCR analyses have confirmed the loss of miR-449 in gastric cancer tissue compared with normal tissue, and miR-449 facilitates translation of p53, p21 as well as the apoptosis markers cleaved *CASP3* and *PARP* by decreasing its oncogenic targets, *MET, CCNE2, SIRT1* and *CDK6*.[91] More details are shown in Table 3 and Figure 2.[92–100]

miRNAs and metastasis of UGICs

MetastamiRs in oesophageal cancer

Invasion and metastasis are critical for cancer progression.[101] In oesophageal squamous cell carcinoma, several upregulated miRNAs (including miR-25[36], miR-92a[37] and miR-205.[52,53]) target *CDH1* to promote EMT. In addition to regulating EMT, many metastamiRs regulate targets that promote invasion and metastasis of tumour cells (Figure 1). miR-10b, which is overexpressed in 95% of

cancers, promotes migration and invasion through the tumour suppressor KLF4 in human esophageal cancer cell lines,[38] while miR-10a controls cell migration and invasion by targeting homebox genes.[53] miR21 is also involved in invasion and metastasis of oesophageal squamous cell carcinoma by targeting *PDCD4 in vitro*; furthermore, patients with oesophageal squamous cell carcinoma with lymph-node metastasis or venous invasion showed higher expression of miR-21 in comparison with **patients without metastasis or venous invasion**. Anti-miRNA-21 transfected cells showed marked reductions in cellular proliferation and invasion.[35] miR-133a targets *CD47* to inhibit tumorigenesis and metastasis *in vivo*.[50] miR-375 inhibits invasion and metastasis by targeting *IGFLR1* and *PDK1*.[47,49] In addition, reduced expression of the miR-143/145 cluster (which regulates *FSCN1*) in oesophageal squamous cell carcinoma is associated with lymph-node metastases.[60] miR-223 inhibits tumour migration and invasion by targeting ubiquitin ligase *FBXW7* and *ARTN* in this cancer.[40,59]

A significant inverse correlation between miR-200 family expression and *ZEB1* and *ZEB2* expression in oesophageal adenocarcinoma has been reported.[24] The expression of three miRNAs has been associated with lymph-node metastasis (miR-99b and miR-199a-3p, and miR-199a-5p).[102]

MetastamiRs in gastric cancer

miR-21 promotes invasion and lymph-node metastasis in gastric cancer.[62,76] miR-196a promotes EMT.[65] Overexpression of mir-196b has been reported to induce migration and invasion by inducing EMT, increasing expression of *VIM* (vimentin) and MMP2, and reducing *CDH1* expression.[103] miR-10b is markedly increased in lymph-node metastasis positive gastric cancer tissues compared with lymphoma node metastasis-free tumor tissues, and were correlated to dowregulation of HOXD10 expression. Functionally, miR-10 overexpression promotes invasion by stimulating RhoC and AKT by targeting *HOXD10*.[104] Upregulation of miR-27 increased the expression of genes associated with EMT, including *ZEB1, ZEB2, SLUG* and *VIM*, while decreasing expression of *CDH1*.[105]

miR-7 has shown anti-metastatic properties by targeting *IGF1R* and *SNAI1* and increasing expression of *CDH1;* hence this pathway could be a potential therapeutic target.[106] miR-145 suppresses tumour metastasis by directly targeting *CDH2* (*N-cadherin*) and *MMP9* but not *MMP2*.[107] miR-409-3p is frequently downregulated in gastric cancer and it reduces tumour cell migration and invasion *in vitro* and metastases *in vivo*.[108] miR-409 targets the pro-metastatic gene *RDX* to suppress metastasis. miR-335 is downregulated in gastric cancer and it targets *BCLW* and *SP1* to suppress tumour cell invasion and metastasis.[109] *ROCK1* promotes invasion and metastasis in many tumour types and miR-148a directly binds to *ROCK1* 3′ untranslated region and inhibits *ROCK1* expression, therefore suppressing metastasis.[110] miR-429 targets *MYC* to inhibit invasion.[82] Overexpression of let-7f can inhibit invasion and migration by targeting *MYH9* (a tumour metastasis associated gene).[111]

Therapeutic implications of miRNAs in UGICs

miRNAS as therapeutic targets

Synthetic miRNA mimics that have been developed for other cancer types include small interfering RNA (siRNA)-like oligoribonucleotide duplexes[112] and chemically modified oligoribonucleotides.[113] miRNAs can be inhibited *in vitro* and *in vivo* by various modified antisense oligonucleotides called antagomiRs; these molecules might, therefore, have a role in cancer treatment. [114] Intensive efforts have been made to develop miRNA-based therapeutics in preclinical models of breast cancer, pancreatic cancer and prostate cancer to modify oncogene or tumour

suppressor functions.[6,115,116] miRNA-based therapeutics are lagging behind for UGICs, but this is a promising area of research.

Modifying chemoresistance

In oesophageal squamous cell carcinoma, cisplatin induces expression of AP-2a, which confers chemosensitivity by promoting apoptosis; AP-2a is a target of the miR-200b/200c/miR-429 cluster, which negatively regulates AP-2a to induce cisplatin resistance.[46] A similar study suggests that overexpression of miR-200c causes cisplatin resistance in oesophageal squamous cell carcinoma cells by upregulating the AKT pathway.[45] miR-141 sensitizes oesophageal squamous cell carcinoma cells to cisplatin by targeting the 3′-untranslated region of *YAP1*, which is known to have a crucial role in apoptosis induced by DNA-damaging agents. [117] miR-148a upregulation in both oesophageal squamous cell carcinoma and oesophageal adenocarcinoma cells increases sensitivity to cisplatin and 5-fluorouracil.[118,119] More detailed studies are needed to elucidate these mechanisms.

The miR-200b/200c/miR-429 cluster sensitized gastric cancer cells (by increasing apoptosis) to vincristine and cisplatin by targeting *BCL-2* and *XIAP*.[99] Overexpression of miR-497 sensitized SGC7901/VCR and A549/CDDP gastric cancer cells to vincristine (VCR), 5-fluorouracil (5-FU), cisplatin (CDDP) by targeting *BCL-2 in vitro*.[97] *In vivo* experiments and subsequent clinical development is needed.

miRNAs as biomarkers in UGICs

Diagnostic markers

miRNAs are stably expressed in serum, plasma, urine, saliva and other bodily fluids,[16] and this property can be exploited. However, little work has been done in this regard in UGICs. In oesophageal squamous cell carcinoma, miR-1322 levels are higher in serum and tumour tissues than in the controls, so this miRNA could serve as a biomarker.[20] OncomiRNAs (miR-21/miR-184/miR-221) and one tsmiR (miR-375) have been studied in the plasma of 50 patients with oesophageal squamous cell carcinoma and 20 healthy volunteers; the plasma level of miR-21 tended to be higher in ESCC patients ($P=0.0649$), while that of miR-375 was significantly lower ($P<0.0001$) and the miR-21/miR-375 ratio was significantly higher ($P<0.0001$) in ESCC patients than in controls.[48]

In gastric cancer, three serum miRNAs (miRs-221/744/376c) could distinguish patients with gastric cancer from healthy controls with 82.4% sensitivity and 58.8% specificity.[120] Moreover, miR-221 and miR-376c demonstrated significantly positive correlation with poor differentiation of GC.[120] In a validation experiment, plasma levels of miR-451 and miR-486 were higher in patients with gastric cancer compared with healthy controls, with high area under the curve (AUC) values (0.96 and 0.92).[121] A genome-wide microRNA profile identified high serum levels of miR-378 in patients with gastric cancer, and validation yielded a high receiver operating characteristic AUC (0.86).[122] A quantitative real-time PCR analysis identified five serum miRNAs (miR-1, miR-20a, miR-27a, miR-34 and miR-423-5p) as biomarkers for gastric cancer, and levels correlated with tumour stage.[123]

Prognostic markers

Although prognostic biomarkers are of less value than predictive or early detection markers, here we describe the literature briefly. miR-21 seems to be a reliable poor prognosticator for oesophageal adenocarcinoma, oesophageal squamous cell carcinoma and gastric cancer.[29,124,125] High levels of miR-92a, miR-99b and

miR-199a in both oesophageal adenocarcinoma and oesophageal squamous cell carcinoma are also poor prognosticators.[102] Reduced expression of miR-375, miR-203 and miR-205 is associated with late stages of oesophageal adenocarcinoma and oesophageal squamous cell carcinoma.[26,30] High serum levels of miR-31 in patients with oesophageal squamous cell carcinoma portend poor prognosis.[41] The serum ratio of miR-21:miR-375 correlates with disease recurrence.[48]

In gastric cancer, overexpression of miR-93 is associated with short survival.[71] Overexpression of miR-10b, miR-107/196a and miR-223 correlates with metastasis status.[76] High expression of circulating miR-17-5p/20a was an independent poor prognostic factor.[75] Low-level expression of Let-7a/let-7g/let-7f are associated with poor prognosis.[87,100] miR-181b and miR-182 are also novel poor prognosticators.[77] Low expression levels of miR-125a-3p were found to be associated with enhanced malignant potential such as tumour size, lymph node and liver metastasis and poor prognosis, and this study suggests miR-125a-3p is a potent prognostic marker in gastric cancer.[126] miR-409-3p was found to be downregulated frequently in patients with gastric cancer, and its expression was associated with distant metastasis.[108] Collectively, many miRNAs demonstrate markedly different expression levels between patients with cancer and control groups, and might serve as prognostic markers for monitoring disease status. However, large case–control studies are needed to validate these individual miRNA markers as useful clinical tools.

miRNAs and cancer stem cells—Emerging evidence indicates that deregulation of miRNAs has an important role in regulating cancer stem cells of organs such as the breast,[127,128] brain (glioma)[129] and prostate.[6] Research to establish the role miRNAs have in regulating cancer stem cells in UGICs is needed.

Conclusions

miRNAs are ubiquitous and plentiful, and are crucial post-transcriptional regulators of human gene expression. Research over the last ten year has identified numerous miRNAs that have diverse roles at multiple steps of tumour progression and metastasis. However, these discoveries have not been translated in to the clinics to help patients with UGICs. Considerably more research is needed, including the demonstration of functional consequences in genetically engineered mouse models. The clinical potential is enormous as miRNAs might provide tools for diagnosis, early detection, prediction and monitoring of therapy, and as therapeutic targets. Overall, this area of research has huge potential and should be actively pursued. Furthermore, discoveries made through the ENCODE (encyclopedia of DNA elements) project seem extremely relevant to miRNA research.[130–133] The interim results of the ENCODE project suggest that only up to 3% of the genome codes for proteins and 76% of the genome codes for RNA elements (including miRNAs), which probably regulate the protein coding genes. Many other discoveries, which are outside the scope of this Review, demonstrate that we must focus on the non-protein-coding genome with the same vigour as we have focussed on the protein-coding genome.

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Biographies

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After obtaining her Ph.D at Biochemistry and Molecular Biology in Beijing University in 1999, she continued her five year's postdoctal fellow training in cancer biology in U.T.M D Anderson Cancer Center. As a result of her academic growth and achievements, she was promoted to Assistant Professor in 2008. During this period, she have actively and productively pursued research of the molecular mechanisms of GI track tumors and have been very astute in identifying areas of GI cancer research which are novel and important especially in the area of esophageal adenocarcinoma.

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Key points

- Worldwide, cancers of the oesophagus, gastro-oesophageal junction and stomach (UGICs) are common and outcomes of patients with UGICs have remained dismal
- miRNAs are non-coding, single-stranded RNAs of ~22 nucleotides and consist of a novel class of gene regulators that negatively regulate their targets.
- Many miRNA have been identified to act as oncogenes, tumor suppressors and important modulators in the process of invasion and metastasis of UGICs.
- Increased activity of oncomiRNAs leads to inhibition of tumour suppressor genes, facilitating cell proliferation and tumour progression; while decreased activity of tumour-suppressor miRNAs (tsmiRs) leads to increased oncogene translation, contributing to tumour progression.
- Certain miRNAs are involved in the regulation of metastasis (metastamiRs) as well as in modulation of chemoresistance in UGICs.
- Circulating miRNAs provide potential biomarkers for ealier diagnosis and prognosis in patients of UGICs.
- Further research could lead to exploitation of miRNAs as therapeutic or diagnostic targets for UCICs.

Review criteria

A literature search was carried out in PubMed for papers published from 2002 to 2012. The search terms used were “miRNA”, “miRNA and Cancer”, “miRNA and esophageal cancer” miRNA and EAC” and “miRNA and ESCC” and “miRNA and GC”. miRNA and cancer progression, apoptosis, metastasis, chemoresistance, target and biomarker were also used as search terms. The search was restricted to English language papers.

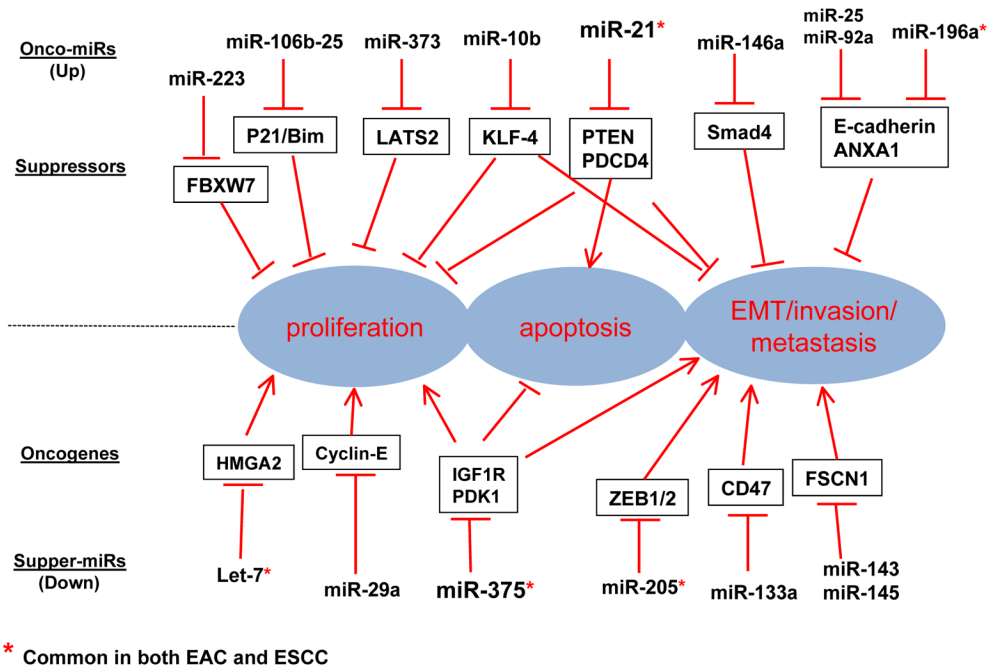

Figure 1.
miRNAs, Targets and functions in Esophageal Cancers
* Common in both EAC and ESCC

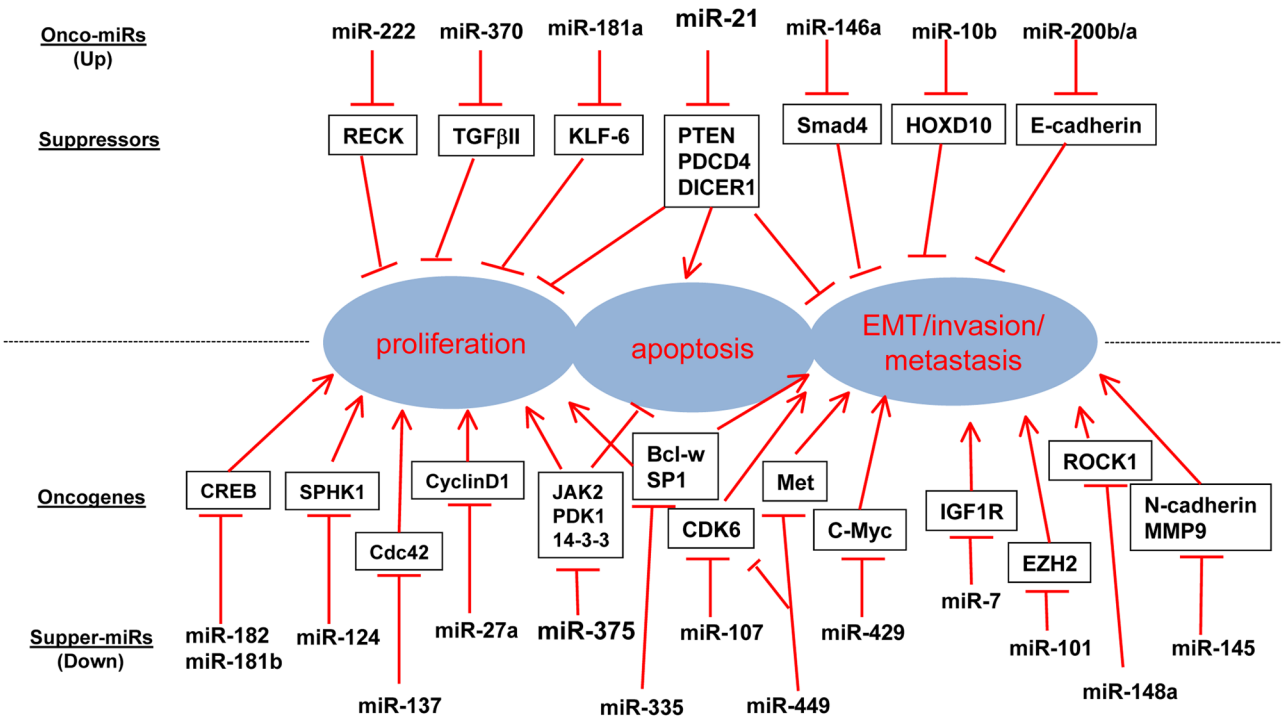

Figure 2.
miRNAs, Targets and functions in Gastric Cancers

Table 1

miRNAs and their targets in oesophageal adenocarcinoma

miRNA	Targets	References
OncomiRs		
miR-21**	PDCD4	21,23,24
miR-196a*	ANXA1/SPRR2C/S100	18,19
miR-192*	NR	26
miR-106b-25	P21/Bim	17
miR-99b/199a	NR	79
miR-194	NR	23
tsmiRs		
miR-203**	NR	24–27,29
miR-205*	NR	24,25,27,29
Let-7a/b/c	NR	28
miR-200a/b/c	ZEB1, ZEB2	20
miR-31/miR375	NR	22
miR-345/494/193a	NR	28

** Reported consistently by more than four individual groups;

* Reported by two groups. Abbreviation: NR, not reported

Table 2

Deregulated miRNAs, potential targets and functions in oesophageal squamous carcinoma

miRNA	Targets	Functions	References
OncomiRs			
miR-21**	PTEN, PDC4	↑Proliferation/invasion	29–31
miR-25	E-cadherin	↑metastasis	32
miR-1322	ECRG2(SPINK7)	↑proliferation	17
miR-223	FBXW7	↑Poor prognosis	37
miR-31	EMP1/KSR2/RGS4	↑Progression	38
miR-92a	E-cadherin	↑Metasta/poor prog.	33
miR-296	CyclinD1, BCL-2	↑Progression	39
miR-10b	KLF-4	↑Migration/invasion	34
miR-373	LATS2	↑Proliferation	35
miR-196a	ANXA1	↑Proliferation	19
miR-129	N/A		40
miR-17-92 cluster	TNF-α	↑Proliferation	41
miR-200c/miR-21	PP2R1B	Cisplatin resistance	42
miR-200b/c/miR-429	AP-2α	Cisplatin resistance	43
TSmiRs			
miR-375**	PDK1, IGF1R	↓growth/metas.	23,36, 38
miR-133a	CD47	↓Lymph node metas.	39,40
Let-7	HMGA2	↓proliferation	6,43
miR-29c	Cyclin E	Cell cycle arrest	47
miR-34a			44–46
miR-223	ARTN	↓Migration/invasion	49
miR-205	ZEB2/EMT	↓Migration/invasion	41,42
miR-141	YAP1	↓Chemo-resistance	97
miR-203	NP63	↓proliferation	57
miR-148a	n/a	↑Chemo-sensitivity	58
miR-210	FGFRL1	Cell cycle arrest	48
miR-205*	E-cadherin	↓Inhibit EMT	49
miR-10a	Homebox gene	↓Migration/invasion	50
miR-143/145 cluster	FSCN1	↓Lymph node metas	59
miR-34a/b/c/129-2			52

** Reported consistently by more than four individual groups;

* Reported by two groups

Table 3

Deregulated miRNAs, targets and potential functions in gastric cancer

miRNA	Targets	Functions	References
OncomiRs			
miR-21**	*PTEN, PDCD4, DICE*	↑ Proliferation/invasion	51–53,80
miR-181a	*R1*	↑ prolif.↓apop.	50
	KLF-6		
miR-196a*	n/a	↑migraton/invasion/EMT	54
miR-93	n/a	Poor prognosis	70
miR-196b	ETS2	↑EMT	55,81
miR-222	RECK	↑ Proliferation	71
miR-10b	HOXD10	↑ invasion/metastasis	82
miR-663	P21		72
miR-146a	Smad4		56
miR-200b/a	E-cadherin	↑EMT	73
miR-27	n/a	↑EMT, metastasis	83
miR-191	NDST1		57
miR-370	TGF-βII		58
miR-223	EPB41L3	↑invasion, metastasis	56
miR-126	SOX2		59
miR-17-5P/20a	n/a	↑ in plasma, marker	74
miR-107/196a/21/9	DICER1	↑lymph node metastasis	75
TSmiRs			
miR-7*	*IGF1R*	↓metastasis	84
Let-7a*	RAB40C	↓CSC	70–72
Let-7f	MYH9	↓invasion, metastasis	89
miR-181b	CREB	Prognostic marker	60
miR-101(microdeletion)	EZH2	↓EMT	62
miR-124	SPHK1	↓proliferation	63
miR-145	N-cadherin, MMP9	↓invasion, metastasis	85
miR-182	CREB	↓proliferation	61
miR-148a	ROCK1	↓invasion, metastasis	88
miR-29a	P42.3		91
miR-335	Bcl-w/SP1	↓invasion, metastasis	87
miR-429	C-MYC	↓ metastasis	65
miR-296	Scribble		66
miR-146a	EGFR, IRAK1	Prognostic marker	92
miR-27a	CyclinD1	↓proliferation	74
miR-10b	MAPRE1		93

miRNA	Targets	Functions	References
miR-375	Jak2, PDK1/14-3-3δ		66,67
miR-622	ING1	↓invasion/migration	94
miR-107	CDK6	↓proliferation/invasion	95
miR-497	BCL2	↑drug sensitivity	96
miR-137 down by methy	Cdc42	↓proliferation	73
miR-449	MET, SIRT1, CDK		74
miR-486	6		69
miR-495/551a	OLFM4	↓invasion/migration	97
miR-409-3P*	PRL-3	↓prolif./metastasis	64,86
miR-200b/c/429 let-7g/miR-34	PHF10, RDX BCL2/XIAP	Drug resistance Chemo-sensitivity/↓CSC	98 99

** Reported consistently by more than four individual groups;

* Reported by two groups