Review Article
MicroRNA single-nucleotide polymorphisms and susceptibility to gastric cancer

Xinhang Jiang, Xintong Chen, Linhua Liu, Huanwen Tang

School of Public Health, Guangdong Medical University, Dongguan 523808, P. R. China

Abstract: Gastric cancer is the second most frequent cause of cancer-related deaths worldwide. MicroRNAs (miR-NAs) are a novel class of endogenous noncoding regulatory sequences that interact with tumor oncogenes and suppressors. Many studies have indicated that single-nucleotide polymorphisms (SNPs) in miRNAs influence the susceptibility of gastric cancer. MiRNA SNPs have been explored for several years as potential biomarkers of gastric cancer. In this review, we discuss five miRNA SNPs (miR-146a rs2910164 G/C, miR-196a2 rs11614913 C/T, miR-149 rs2292832 T/C, and miR-27a rs11671784 G/A and rs895819 A/G) to illustrate the achievements in this field and to stimulate further research. We also mention three other gastric-cancer-associated miRNA SNPs (miR-34 rs4938723 T/C, miR-107 rs2296616 T/C, and miR-214 rs114673809 G/A).

Keywords: Gastric cancer, microRNA, single-nucleotide polymorphism, genetic susceptibility

Introduction

Gastric cancer is the fourth most common cancer in the world, and has the second highest cancer-related mortality rate [1, 2]. The causes of gastric cancer vary, and include personal genetic susceptibility, lifestyle factors, and environmental factors. However, some researchers have found that only a minority of the population exposed to these risk factors ultimately develops gastric cancer [3, 4]. Therefore, genetic susceptibility may play a significant role in the development of gastric cancer [5, 6]. Single-nucleotide polymorphisms (SNPs), a major type of genetic variant, have been widely investigated as molecular markers with which to predict the initiation, treatment outcomes, and prognosis of gastric cancer. Recently, miRNA SNPs have been reported in several studies.

MiRNAs are a kind of endogenous noncoding RNA, 19-25 nucleotides long, that regulate cell multiplication, differentiation, and apoptosis by binding to the 3'-untranslated regions of messenger RNAs (mRNAs) to cause mRNA degradation or inhibit translation [7-9]. One-third of the human genome is reportedly regulated by miR-NAs [10]. The conservation, temporal expres-

sion, and tissue specificity of miRNAs make them excellent candidate molecules for the development of novel biomarkers for the early diagnosis and prevention of cancer [11-14]. Increasing evidence also suggests that SNPs in miRNAs influence the expression or function of mature miRNAs, thus altering an individual's susceptibility to gastric cancer [4, 5, 15]. In this short review, we discuss eight miRNA SNPs that are all associated with gastric cancer, including five miRNA SNPs with more publications and three other miRNA SNPs with less publications (**Table 1**).

miR-146a rs2910164 G/C polymorphism and gastric cancer

It has been reported that miR-146a is associated with cancer because it regulates the expression of interleukin receptor associated kinase (IRAK1), tumor necrosis factor receptor-associated factor 6 (TRAF6), and nuclear factor kappaB (NF-κB) [16]. The miR-146a rs2910164 G/C polymorphism associated with gastric cancer has been studied by several teams. Zeng et al. demonstrated that the miR-146a (GC + GG) genotype entailed a significantly higher risk of gastric cancer in a Chinese population than the CC genotype (odds ratio [OR] = 1.58; 95% confi-

Table 1. MiRNA single-nucleotide polymorphisms (SNPs) in gastric cancer

miRNA	SNP ID	Allele	Adjusted OR (95% CI)	Population	References
miR-146a	rs2910164	G/C	1.58 (1.11-2.20)	Chinese	[17]
			1.26 (1.01-1.56)	Chinese	[18]
			2.69 (1.29-5.62)	Korean	[19]
			1.30 (1.02-1.66)	Japanese	[20]
			NS	Japanese	[21]
			NS	Japanese	[22]
miR-196a2	rs11614913	C/T	1.57 (1.03-2.39)	Chinese	[23]
			1.86 (1.09-3.19)	Korean	[19]
			1.50 (1.02-2.22)	Japanese	[22]
			14.80 (8.09-27.09)	Greek	[24]
			0.71 (0.60-0.83)	Chinese	[25]
			NS	Japanese	[20]
miR-149	rs2292832	T/C	0.68 (0.44-1.04)	Chinese	[26]
			2.29 (1.25-4.22)	Greek	[24]
miR-27a	rs11671784	G/A	0.809 (0.697-0.911)	Chinese	[11]
			0.68 (0.49-0.94)	Chinese	[27]
	rs895819	A/G	1.48 (1.06-2.05)	Chinese	[28]
			1.43 (1.01-2.02)	Chinese	[27]
miR-34b/c	rs4938723	T/C	0.75 (0.57-0.99)	Chinese	[29]
miR-107	rs2296616	T/C	0.39 (0.31-0.49)	Chinese	[30]
miR-214	rs114673809	G/A	1.667 (1.044-2.660)	Chinese	[31]

NS: no significant association.

dence interval [CI], 1.11-2.20) [17]. Another study conducted by Zhou et al. in 1686 gastric cancer patients and 1895 cancer-free subjects showed that individuals with the G polymorphism had a significantly elevated risk of gastric cancer (OR = 1.26; 95% CI, 1.01-1.56) [18]. According to Ahn et al., the GG genotype was significantly associated with an increased risk of gastric cancer in a small nonsmoking Korean sample [19]. However, studies in the Japanese population have had different results. One suggested that the CC genotype entailed a significantly higher risk of gastric cancer (OR = 1.30; 95% CI, 1.02-1.66) [20], whereas in other studies, miR-146a rs2910164 G/C did not correlate with gastric cancer [21, 22]. These inconsistent results might be attributable to underpowered sample sizes and ethnic differences.

miR-196a2 rs11614913 C/T polymorphism and gastric cancer

The study conducted by Peng et al. on 213 gastric cancer patients and 213 controls from a Chinese population suggested that miR-196a2 rs11614913 CC homozygotes had a significantly higher risk of gastric cancer than the TT or TC genotype (OR = 1.57; 95% CI, 1.03-2.39) [23]. A study of 461 patients and 447 cancer-free controls showed a higher risk of gastric cancer among women with the miR-196a2 CC genotype in a Korean population (OR = 1.86, 95% CI, 1.09-3.19) [19]. Recently, a case-control study in elderly Japanese revealed that the CC genotype of the rs1161493-13 polymorphism was significantly associated with an elevated gastric cancer risk (OR, 1.50; 95% CI, 1.02-2.22) [22]. Dikeakos et al. also found a significantly higher risk of gastric cancer in those with the miR-196a2 rs2292832 CC genotype (OR = 14.80, 95% CI, 8.09-27.09) [24]. However, in contrast to the results described above, Wang et al. found evidence that CC homozygotes had a significantly lower risk of gastric cancer than individuals with the TT or TC genotype in a large sample of the Chinese population (CC vs. TC + TT: OR = 0.71; 95% CI, 0.60-0.83) [25]. Another study showed that in a Japanese population, the miR-196a2 SNP only correlated with the degree of *Helicobacter pylori*-induced mononuclear cell infiltration, and was not associated with gastric cancer [20].

miR-149 rs2292832 T/C polymorphism and gastric cancer

A case-control study including 762 cases and 757 controls, who were all Chinese, was conducted by Zhang et al. In that study, the miR-149 rs2292832 T-to-C polymorphism showed a significant protective function against gastric cancer in males (TC + CC vs. TT: OR = 0.68; 95% CI, 0.44-1.04) [26]. However, another study based on a Greek population, which included 163 patients and 480 controls, sho-

wed contrary evidence, in that the miR-149 rs2292832 CC homozygotes displayed a significantly increased risk of gastric cancer (OR = 2.29; 95% CI, 1.25-4.22) [24].

miR-27a rs11671784 G/A and rs895819 A/G polymorphisms and gastric cancer

The SNPs in miR-27a have been investigated in recent years, and several studies have shown that miR-27a rs11671784 G/A and rs895819 A/G both correlate with gastric cancer. To clarify the association between miR-27a rs11671784 and gastric cancer, Yang et al. examined 892 gastric cancer patients and 978 cancer-free control subjects, and showed that the A allele correlated significantly less strongly with the occurrence of gastric cancer than the G allele (OR = 0.809; 95% CI, 0.697-0.911), indicating that the A variant exerts a protective effect against gastric cancer [11]. Recently, this was confirmed in a Chinese population when Song et al. verified the results of Yang et al. in 278 gastric cancer patients and 278 healthy matched subjects in a case-control study (OR = 0.68; 95% CI, 0.49-0.94) [27].

Another study showed that the miR-27a rs895819 A/G SNP significantly increased the risk of gastric cancer when the variant genotypes were compared with the AA homozygotes (OR = 1.48; 95% CI, 1.06-2.05) [28]. Song et al. also found that individuals with the miR-27a rs895819 AG and GG genotypes had a 1.43-fold higher risk of gastric cancer than those with the AA genotype (OR = 1.43; 95% CI, 1.01-2.02) [27].

Some other gastric cancer-associated miRNA SNPs (miR-34b/c rs4938723 T/C polymorphism, miR-107 rs2296616 T/C polymorphism, and miR-214 rs114673809 G/A polymorphism)

The study of 419 gastric cancer patients and 402 cancer-free controls conducted by Yang et al. suggested that the wild-type TT genotype of miR-34b/c rs4938723 significantly reduced the risk of gastric cancer compared with the variant genotypes CT and CC (OR = 0.75; 95% CI, 0.57-0.99) [29]. According to Wang et al., the TC and CC genotypes of the miR-107 rs2296616 SNP were significantly associated with a reduced risk of gastric adenocarcinoma (OR = 0.39; 95% CI, 0.31-0.49) in a large

Chinese sample [30]. Another study genotyped the miR-214 rs114673809 SNP in 345 gastric cancer patients and 376 cancer-free controls in a Chinese Han population, and showed that AA homozygosity conferred a significantly increased risk of gastric cancer (OR = 1.667; 95% CI, 1.044-2.660) [31].

Conclusion

There are still many challenges in the study of gastric-cancer-associated miRNA SNPs. The patient samples are small, with insufficient statistical power to prove an association between miRNA SNPs and gastric cancer. The explored population is also not sufficiently wide. More extensive and wide-ranging data on miRNA SNPs from many countries are required. The exact mechanisms of miRNA SNPs also remain a mystery. For example, it is unclear whether miRNA SNPs interact with other SNPs.

The conservation, temporal expression, and tissue specificity of miRNAs makes miRNA SNPs potentially perfect diagnostic and prognostic biomarkers, which may reduce the frequency of cancer or even greatly improve patients' prospects of survival. Recent studies of other non-coding RNAs (long noncoding RNAs and circular RNAs) have all shown significant associations with miRNA, so it seems that miRNAs are among the most essential biological molecules. Therefore, more extensive research into miRNA SNPs is required.

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Address correspondence to: Huanwen Tang, School of Public Health, Guangdong Medical University, Xincheng Road 1, Dongguan 523808, P. R. China. Tel: +86 769 22896569; E-mail: 545596441@qq.com

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