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MINIREVIEWS

Role of microRNAs in the predisposition to gastrointestinal malignancies

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Abstract

MicroRNAs (miRNAs) are highly deregulated in cancer and play a role in the initiation of tumorigenesis. Recently, miRNAs have attracted attention in gastrointestinal (GI) cancers. Single nucleotide polymorphisms (SNPs) could affect the genes involved in each step of miRNA biosynthesis. Several meta-analyses of case-control studies have assessed the association between miRNA "pathway" gene-SNPs (including biosynthesis regulators and binding sites) and susceptibility to GI cancers. We present in this mini-review the current knowledge on the association between miRNAs "pathway" genes and GI cancer predisposition. The interaction between miRNA/regulators/binding site-SNPs and environmental as well as genomic factors is an interesting field that should be exploited in future studies.

Key words: Cancer; Digestive tract; MicroRNA; Review; Risk; Single nucleotide polymorphism

Core tip: We discuss in this mini-review the current knowledge on the association between microRNA-gene-single nucleotide polymorphisms as well as their regulators/binding sites and gastrointestinal cancer predisposition. They could act as tumor suppressors as well as oncogenes depending on their target. We also discuss the interaction between microRNAs and environmental factors and genomic susceptibility like microsatellite instability.

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INTRODUCTION

MicroRNAs (miRNAs) are highly conserved short (nearly 20 nucleotides) non-coding RNA-molecules that control cell survival and proliferation. In their biologically active form, they induce the downregulation of mRNA. A single miRNA can regulate the expression of many mRNA-targets involved in different biological pathways[1]. Hence, even a small change in their structure and activity can have a profound effect on cell homeostasis. Studies have shown that key miRNAs are highly deregulated in cancer and play a role in the initiation of tumorigenesis by influencing the expression of oncogenic and tumor suppressor proteins[1,2].

To date, more than 2000 sequences of miRNAs have been reported in humans[3,4], and more than 4500 miRNA gene-variations have been described. Single nucleotide polymorphisms (SNPs) of miRNA-related genes have been shown to increase cancer risk and have attracted attention in recent years mainly in gastrointestinal (GI) cancers[5].

This mini-review intends to present the current knowledge on the association between SNPs affecting miRNAs as well as their machinery genes and the risk of developing GI cancers.

THE MIRNA FROM PRODUCTION TO ACTION

The regulation of miRNA biosynthesis is complex and under continuous investigation[6]. miRNA genes are generally transcribed by RNA polymerase II from intergenic regions of the genome, though they can be found in coding areas (intragenic) as well. Most are transcribed independently form another, but some show a tandem repeat-like cluster organization[7]. After DNA transcription, the resulting pri-miRNAs are cleaved in the nucleus into small sequences (nearly 60 nucleotides) by DROSHA ribonuclease III enzyme and its cofactor DGR8. After their export to the cytoplasm by exportin-5 (XPO5), the pre-miRNAs are processed by DICER ribonuclease into a mature duplex. The next step is the unwinding which consists in the separation of the two miRNA brands, followed by loading of the brand containing the seed region onto RNA-inducing-silencing complex (RISC). These complex guide mature miRNAs to 3'UTR region of their target mRNA-sites resulting in their cleavage and translational repression[8]. Figure 1 illustrates the structure of pri, pre, and mature miRNA.

MIRNA AND MACHINERY GENE SNPS AND GI CANCER RISK

Recent studies have shown that key miRNAs could act as tumor suppressors or as oncogenes in GI cancers depending on their targets[1]. Potential tumour suppressor miRNAs include among others miRNA-15b and miRNA-16 which modulate apoptosis *via* targeting BCL2 in gastric cancer (GC)[9], and miRNA-34a *via* E2F pathway in colorectal cancer (CRC)[10]. Potential oncogenic miRNAs include among others miRNA-21 *via* PTEN in hepatocellular carcinoma (HCC)[11], GC and CRC[12]; miRNA-106a *via* RB1 in CRC[12]; miRNA-106b-25 cluster *via* TGF-beta in GC[13]. SNPs could affect genes involved in each step of the miRNA biosynthesis including miRNA-binding sites as well as their regulators, consequently impacting their function (gain or loss) (Figure 2)[14].

MIRNA SNPS

Several meta-analyses of increasing number of case-control studies have been conducted to assess the association between different miRNA-polymorphisms and GI cancer susceptibility[5]. We present in this minireview four miRNA SNPs that are, to our opinion, the most validated to date as risk factors for GI cancers. These include miRNA-146a rs2910164, miRNA-149 rs2292832, miRNA-499a rs3746444 which affect

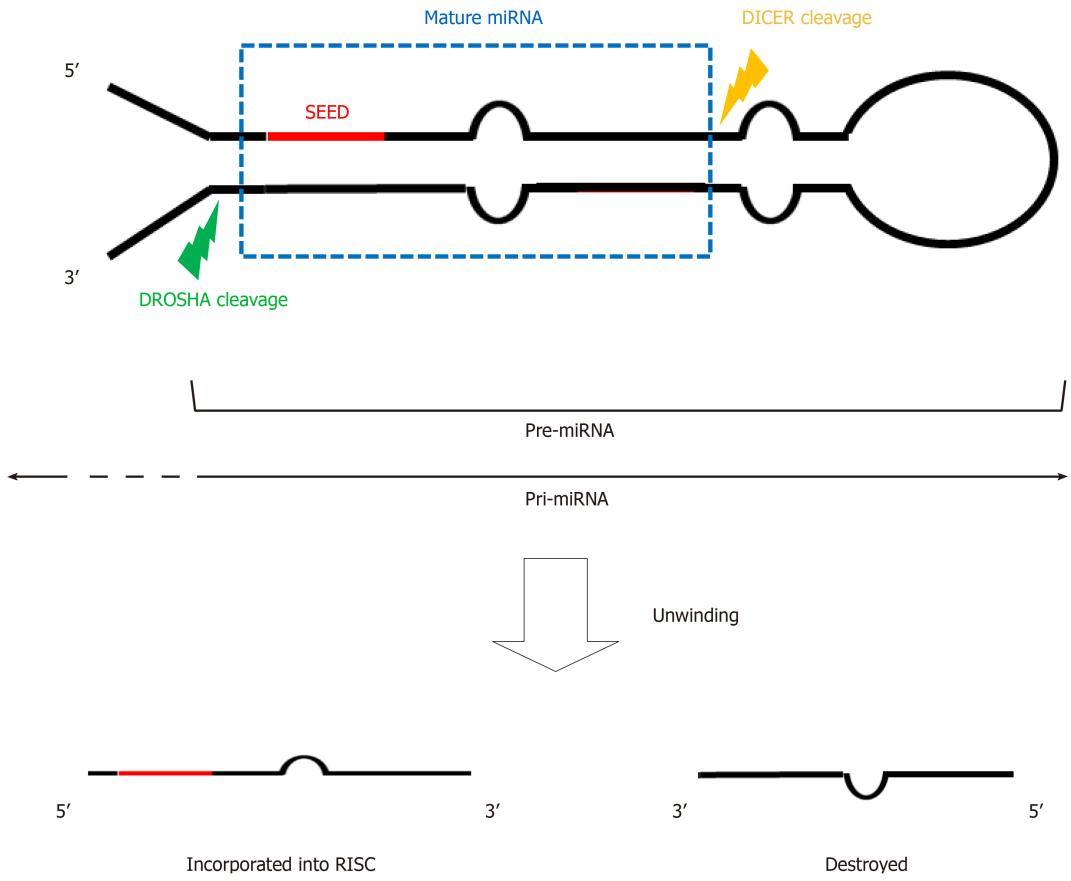

Figure 1 The hairpin-like structure of miRNA and its' precursors (pri-miRNA and pre-miRNA).

the seed region, as well as miRNA-196a2 rs11614913 affecting the premature form[5].

miRNA-146a belongs to a family of miRNAs involved in the regulation of inflammation and the innate immune system[15]. It has been associated with tissue invasion and metastases as well as independence on external growth factor signals[2]. Multiple target-sites for miRNA-146a have been identified and include the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), the CCAAT enhancer-binding-protein-β (C/EBPβ), and the interferon regulatory factor 3/7 (IRF3/7)[16]. miRNA-146a rs2910164 (C>G) polymorphism which affects the seed region[5], was closely associated with GI cancers especially GC[17,18], CRC[17], and esophageal[18] cancer as well as HCC mainly in Asian populations[19]. The odds ratio (OR) ranged between 1.1 and 1.2 (increased risk of 10% to 20%). Members of the mi-RNA 196 family are in the region of the homeobox (HOX) genes (HOXC 9-10 specifically for miR-196a-2 gene), which are transcription factors essential for embryonic development. The non-histone chromatin-binding protein HMGA2 (for High-mobility group A2) mRNA was identified as one of its most important putative targets[20]. This later has been shown to play an important role in cancer metastases and epithelial-mesenchymal transition (EMT)[21]. rs11614913 (C>T) affects the mature form of mi-RNA196a2 and potentially impact the protein-coding region of HOXC6[5]. Studies have suggested an increased risk of CRC in Asian populations (increased risk between 20%-30%)[22,23], and GC in both Asians and Caucasians[14]. A third SNP affecting the seed region is the mi-RNA-499a rs3746444 (A>G) which could impact the protein-Coding MYH7B. This SNP has been shown to increase the risk of esophageal cancer in Iranian and Chinese populations[5,24].

rs2292832 (T>C) affects the premature form of the pro-apoptotic miRNA-149 which is known to inhibit the expression of Akt1 and E2F1[25]. This SNP has been associated with CRC mainly in Asian populations with an increased risk of 20%[26].

SNPS IN MACHINERY GENES AND BINDINGS SITES

MiRNA-machinery-gene polymorphisms could also impact the biosynthesis and activity of miRNAs. Several SNPs have been studied affecting DROSHA, DICER, DGCR8, XPO5 as well as several other regulators with conflicting results. As an

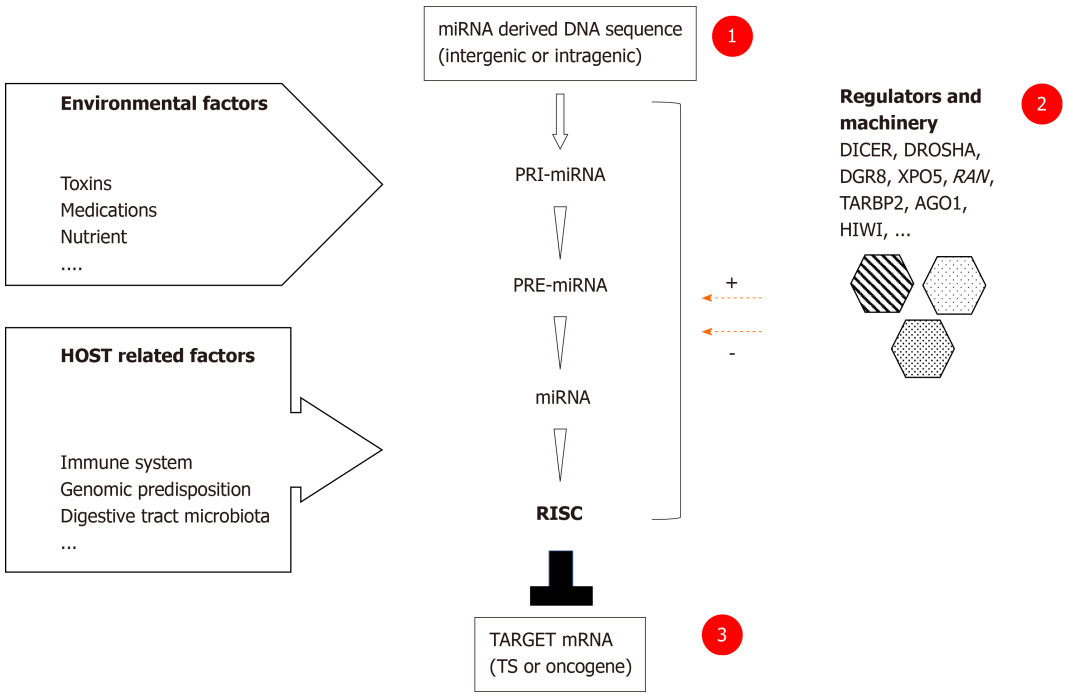

Figure 2 Schematic illustration summarizing the miRNA "pathway" including miRNA biosynthesis, processing and mRNA inhibition by RNA inducing silencing complex. Numbers in red define the three sites potentially affected by single nucleotide polymorphisms as well as their interaction with environmental and host-related factors. +: Activation; -: Inhibition; RISC: RNA inducing silencing complex.

example, XPO5 rs11077 (A→C) affects the activity of miR-617 and miR-4763–5p, and has been associated with CRC in Asian patients with hypertension[27] as well as esophageal cancer in Caucasian patients[28]. On the other hand, a meta-analysis including 10 case-control studies has analyzed the association between DROSHA/DGCR8 SNPs and cancer risk. Only HCC cases had been analyzed among GI cancers, and had not been associated with any of the studied SNPs[6].

SNPs affecting miRNA targets have also been suggested to affect GI cancer risk especially those located in the binding sites of miRNAs. rs12947947 (G>A) and rs28363292 (T>G) located in the 3′UTR of *RAD51D* have been jointly associated with an increased risk of HCC (nearly 1.5 times) mainly in Zhuang people (nearly 3 times) compared to controls[29]. Other target sites have also been studied including INSR T>C (rs1051690)[30] and CD133 rs2240688 A>C in GC[31].

INTERACTION WITH ENVIRONMENTAL FACTORS AND GENOMIC SUSCEPTIBILITY

The increased risk of GI cancers owing to SNPs could be potentiated by the interaction with environmental factors affecting miRNAs. As an example, it has been shown that long-term colonization of *H. pylori* might affect the activity of different miRNAs in gastric mucosae through epigenetic modifications[1,32,33]. miRNAs that are down-regulated in response to *H. pylori* include several components of the Let 7 family (which control cell cycle progression, proliferation, and invasion *via* RAB40C and HMGA2), miRNA-101 (proliferation, apoptosis, invasion and migration *via* COX-2, FOS, MCL1, EZH2), miRNA-141 (cell proliferation *via* FGFR2), miRNA-203 (proliferation, invasion *via* ABL1), miRNA-218 (proliferation, apoptosis, invasion and metastasis *via* ECOP and ROBO1), miRNA-375 (proliferation, apoptosis *via* PDK1 and JAK2), miRNA-449 (cell cycle progression and proliferation *via* GMNN, CCNE2, MET and SIRT1). On the other hand, up-regulated miRNAs include miRNA-17 (cell cycle progression *via* p21), miRNA-20a (cell cycle progression via p21), miRNA-21 (proliferation, apoptosis and invasion *via* PDCD4, RECK and PTEN), miRNA-146a (proliferation, apoptosis and immune response *via* IRAK1, TRAF6 and SMAD4), miRNA-155 (apoptosis and immune response *via* IKK-ε, SMAD2, FADD and PKI alpha) and miRNA-223 (invasion and metastasis *via* EPB41L3)[34,35].

Furthermore, accumulating evidence has supported the hypothesis of an interaction between miRNA-machinery and microsatellite instability (MSI) in the pathogenesis of GI cancers. As an example, miRNA-155 has been shown to

downregulate the expression of MLH1, MSH2, and MSH6, whereas XPO5 has been found to be mutated in MSI + GI cancers[36].

CONCLUSION AND FUTURE PERSPECTIVE

In conclusion, SNPs affecting miRNA "pathway" genes (including regulators and binding sites) could have an impact on GI cancer susceptibility. However, as shown above, most meta-analyses have included only case-control studies which were mainly realized in Asian populations. To our knowledge, no prospective study has been published yet. Furthermore, even in studies where the risk of GI cancers has been found to be increased by a specific SNP, the magnitude of association was low (OR between 1.1 and 1.3) and varies according to different factors like ethnicity.

In our opinion, the interaction between miRNA/regulators/binding site SNPs and environmental factors as well as genomic susceptibility, like MSI, is an interesting field that should be exploited in future studies.

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