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Effects of microRNAs polymorphism in cancer progression

Simin SiamiGorji[1], Isa Jorjani[1], Alireza Tahamtan[2], Abdolvahab Moradi*[2]

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Abstract

MicroRNAs (miRNAs) are known as a new class of small RNAs (18-25 nucleotides) that regulate gene expression at multiple levels from transcription to translation. Considering the important role of miRNAs in cell proliferation, differentiation, and apoptosis, any variations in their expression can contribute to various anomalies, such as tumorigenesis. Single-nucleotide polymorphisms (SNPs) have received much attention as potential genetic markers for diseases due to their advantage of being present at a high frequency in the human genome. SNPs can occur in different parts of the miRNA genes (primary, precursor, and mature) which result in pathological conditions. In this study, recent findings related to the effects of SNPs in miRNAs on their biogenesis and functions and their role in cancer development and progression are discussed. This review was performed using PubMed to search for related reports. The identified effects may be useful for clinical decision-making and providing important new information about the pathophysiology of miRNAs.

Keywords: MicroRNAs, Noncoding RNAs, Single nucleotide polymorphisms, Mutation, Cancer

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Introduction

Nearly 1.5% of the human genome is transcribed and translated to protein, and this process leads to creation of a wide variety of noncoding RNAs (ncRNAs), such as microRNAs (miRNAs), long noncoding RNAs (lncRNAs), rRNAs, and tRNAs (1). Also, miRNAs are identified in eukaryotes and attach to the regulatory elements of target mRNA. They tend to negatively regulate the expression of a large number of target genes through the degree of complementarity between the miRNAs and the target genes. Moreover, miRNAs are able to intensify the expression of target genes and regulate transcription and translation. Changes in miRNA s that lead to abnormalities are categorized in 2 ways: The first category is the variation of the cis factors, such as chromosomal changes, epigenetic changes, mutations in the promoter elements, and polymorphism in the miRNA sequence. The second category is changes in transfactors, such as polymorphism in the target genes, mutation in the regulatory and processing elements (2).

Single-nucleotide polymorphisms (SNPs) are the most common and prevalent genetic variation that can affect miRNAs function. It is thought that SNPs in miRNA af-

Corresponding author: *Dr Abdolvahab Moradi, abmoradi@goums.ac.ir*

1. Department of Biology, Faculty of Basic Science, Gonbad Kavous University, Gonbad kavous, Golestan, Iran
2. Department of Microbiology, School of Medicine, Golestan University of Medical Sciences, Gorgan, Iran

↑What is "already known" in this topic:
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→What this article adds:
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fect miRNAs function in different levels: SNP in Pri-miR (primary-miRNA), SNP in Pre-miR (precursor-RNA), SNP in miRNA biogenesis genes, SNPs in mature miRNA sequences, and mRNA binding-site (3). While it is believed that single mutations do not directly affect the expression of cancer cells, recent studies have shown that the small changes in miRNAs can affect tumorigenesis. It has been proposed that SNPs in miRNAs play a role in the genes processing machines, binding status, cancer treatment quality, and prognosis of patients (4). Despite the key role of genetic changes in the development of tumors, no comprehensive study has been reported in the literature on this subject. This review discusses whether subtle changes, such as SNPs in different sequences of miRNAs, have different effects on the activity of the miRNAs, cell function, and cancer formation.

miRNAs and tumorigenesis

Cancer is caused by accumulation of genetic changes and subsequently inactivation of tumor suppressor genes (TS-genes) and protoncogens activation. Some special miRNAs serve as a tumor suppressor (TS-miR) and oncogene (onco-miR), thus, their downexpression and overexpression interfere with tumor susceptibility. Deregulation of miRNAs expression through destroying cellular arrangement in normal tissues leads to malignant formation, which results from different mechanisms, e.g., chromosomal abnormalities, epigenetic changes, alterations in the miR-processing machinery, and genomic mutations /polymorphisms (5).

Chromosomal abnormalities

About half of human miRs genes and clusters exist in (or around) the chromosomal fragile site (FRAs) and cancer-associated genomic regions (CAGRs). FRAs are prone to genomic instability events, such as chromatid exchange, translocation, deletion, amplification, and copy number variation (CNV). These events might change miRs correct sequence and structure or their target dosage, therefore interfere with normal gene regulation and cause abnormalities (6). Some miRs beside Dicer and Drosha were subjected to CNVs and repeatedly proliferated in NSCLC (nonsmall cell lung cancer) (7).

Epigenetic changes

The regulatory effect of epigenetic on miRs has been achieved through DNA hyper methylation, hypo methylation, and destruction of histone modification patterns in human tumors. In other words, tumor formation might be due to epigenetically silenced TS-miRNAs or activated oncomiRs by aberrant hyper and hypo methylation of CpG islands located around these genes, respectively or by posttranscriptional modifications of nucleosomal histone proteins modifications (8).

Alterations in the miRNA processing machinery

The biogenesis of miRs in tumor samples is different from normal ones. There is a decreasing expression of Dicer and Drosha in various types of cancer. In fact, the precise location and direction of Drosha cleavage for creating a mature miRs is very important, because the second cleavage occurs at a certain distance from the free end (9). Any variation which leads to down/overexpression of miRs biogenesis genes in the cell directly changes the miRs expression and indirectly alter their targets in different tissues.

Genomic mutations and polymorphism

The mutation and polymorphism in miRs transcript can affect their expression by altering the processing or sequence of miRs (6). This finding confirms that every aberration in miRs expression can be the cornerstone of genetic deregulation and carcinogenic. In this review, the SNPs were categorized and the effect of SNPs in miRs sequence, miRs-processing genes, and miR-target-site and miRs regulatory elements were determined.

The effects of miRNAs on cellular microenvironment

One of the major characteristics of tumorous cell is deregulation of gene networks that cause alteration in normal cells. Cellular microenvironments cover a high range of cell types, such as the extracellular matrix (ECM), stromal cells, and stem cells. They can play as “game changer” which may affect the progression phase of malignancy or maintain it in silent stage. Correlation between the microenvironment cells in the vicinity of tumor cells is arranged by miRNAs. miRNAs have 2 key roles in the evolution of tumor microenvironments from normal cells: miRNAs in tumor cells recruit noncell mechanism autonomously to modify microenvironments, and they fixate oncogenic properties. Angiogenesis, invasion, and tumor-stromal interactions are results of miRNAs’ regulation (10).

Effect of SNPs on miRNAs

Heterogeneous distribution of SNPs across the genome leads to more aggregation in noncoding regions than coding regions. A large number of SNPs located in the noncoding regions of the genome are functional including the miRNAs and their target sites. Indeed, these SNPs change the level of gene expression instead of altering the protein's performance (11). miR-SNPs are often found in QTL (quantitative trait loci), chromosomal FRAs, and tumor potential sites, indicating their ability to genetically control complex characteristics. There are several methods to show the effect of human abnormality-related SNPs on miRs expression level: I. SNPs in miRs biogenesis pathways, which interfere with miRs-processing; II. SNPs in miRs sequence interfere with maturation process; and III. SNPs in miRs’ promoter and target genes, which change the expression levels and lose the binding efficiency to miRs (12).

The consequences of SNPs in miR sequences are aberrant expression of hundreds of genes and pathways (3). For instance, some studies demonstrated that most SNPs in miRs (pre/mature) changed targets expression level via changing mature-miRs frequency (13). Mature-miR SNPs are classified into 2 subgroups: 1. SNPs in 5’-seed region affect target recognition and stability of miR-mRNAs interaction; 2. SNPs in 3’-mismatch tolerant region that may withstand mismatch (3). Seed-SNPs interfere with pri to pre-miR conversion and also post-transcription regulations via altering miR-target sites (13, 14). Some seed-SNPs that are phenotypically neutral, facilitate miRs’ evolution

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toward new miRs with more specialized operation. Principally, miRs variations can eliminate binding to key targets and create a seed sequence which targets new mRNAs, changing the regulatory growth proteins balance (14).

Effect of SNPs on 3'UTR of miR-target genes in cancers

The 3'untranslated regions (3'UTRs) are involved in various levels of mRNA in the regulation of genes expression. Also, 3'UTR-SNPs, as miRs-binding site, by modifying the regulatory loops between them cause genetic changes, and subsequently trigger malignancies. In fact, by changing polyadenylation, mRNA-miRNA and mRNA-protein interaction influence mRNA stability and translation. The effect of 3'UTR-SNPs on changing target sequence and target's second structure has been surveyed. The degree of alteration in mRNA second structure show the possible availability for miRs-targeting which has been used in predicting the creation or degradation of the miR-binding-site (15). In this regard, 2 categories are provided: 3'UTR-SNPs, which make illegitimate-miR target sites, can cause tumor risk dependent on TS-miRs, or oncomiRs (16-19). 3'UTR-SNPs which destroy miR-binding position are associated with cancer susceptibility (18-21) (Table 1). These achievements indicate the importance of abnormality-associated-SNPs located in UTR within or near the miRs-binding sites in various cancers.

Effect of SNPs on miRNAs' sequence in cancer

Generally, miRs are divided into 4 groups based on genomic location related to intron and exon: (1) intronic miRs in ncRNA transcripts; (2) intronic miRs in protein-coding genes; (3) exonic miRs in ncRNA transcripts, such as miR-22 and miR-198; and (4) exonic miRs in protein-coding genes. For instance, miR-985 is found in the last exon of CACNG8 gene (22). Also, miRs placed in noncoding regions between genes are called intergenic. Noncoding SNPs refer to those which occur in noncoding gene regions, including miRs sequence, regulatory regions, intronic and intergenic regions presence in coding genes. MIRs-related-SNPs that involve in tumorigenesis can also exist in miR's host genes, which encode tumor-related proteins (23).

SNPs in miRNAs found in introns of protein-coding genes

A separate evaluation of miRs based on origin explicitly addresses the SNPs presence in miRs and their possible association with various tumors. Accordingly, rs928508 in intronic-mir-30c1 (24) reduces mature and pre-miR-30c level in NSCLC through heterogeneous genotypes (AG/GG) (25). The homozygous genotype of this polymorphism also results in altered miRNA expression by altering miRNA structure, which has been observed in gastric cancer (26). Table 2 displays other examples of intronic miRs as such, SNP, which interfere with miR maturation (27-30).

SNPs in miRNAs found in introns of noncoding transcription units

Sometimes, transcription units, which lack the ability of coding protein, serve as a location for a number of intronic-miRs. ncRNAs transcripts are sometimes known as mRNA-like-ncRNAs (mlncRNAs) because they share common characteristics with mRNAs such as splicing and polyadenylation. A to C SNP in miR-30c-2, as an instance of this group (24), may be effective in target gene-selecting and inefficient miR processing, if located in mature miR and pri-miR, respectively (31). Some examples of miRs in intronic ncRNAs accompanied by related SNPs are presented in Table 2. In fact, many studies have determined the SNPs influence on miR frequency and predisposition to various cancers risk (32-35).

SNPs in miRNAs located in exons of noncoding transcription units

Approximately, 10% of miRs are encoded in exonic regions (22). ncRNAs, whose only important activity is acting as miR-host gene, contain many exonic miRs (24). The exonic miRs are transcribed in pri-miRNAs and include 5'-cap and 3'-polyA. A vivid example of this group is miR-155 derived from the third exon of BIC transcript; namely, mlncRNAs. Natural functional SNPs in loop region and miR-155* change the second structure of miR-155 in humans (36). Although the effects of these SNPs have been identified on mature miR expression and immunological response in humans, their relation to cancer has not been studied until now. Also, information on stud-

Table 1. Effect of SNP in miR-target genes on cancers

Target gene	miRNAs	SNP	Position	Type of SNP	Effect of SNP	Cancer	Reference
TYRP1	miR-155	rs683/rs910	3′UTR	non-coding	Illegitimate miR-target site	Melanoma	(16)
KIT	miR-221 miR-222	rs17084733	3'UTR	non-coding	Illegitimate miR-target site	Thyroid	(17)
RPA2	miR-3149 miR-1183	rs7356	3′UTR	non-coding	Illegitimate miR-target site	Colorectal	(18)
ARHGAP26	miR-18a-3p	rs187729	3'UTR	non-coding	Illegitimate miR-target site	ALL, CML	(19)
TLX1	miR-492	rs2742038	3′UTR	non-coding	Illegitimate miR-target site	ALL	(19)
IRF8	miR-330	rs10514611	3′UTR			CML	
KRAS	let-7	rs61764370	3′UTR	non-coding	Target-site destruction	Ovarian	(20)
GTF2H1	miR-518a miR-527	rs4596	3′UTR	non-coding	Target-site destruction	Colorectal	(18)
ETV6	miR-34c miR-449b	rs1573613	3′UTR	non-coding	Target-site destruction	ALL	(19)
ESR1	miR-453	rs2747648	3′UTR	non-coding	Target-site destruction	Breast	(21)

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Table 2. Effect of SNP in miRNAs on various cancer

miRNA	Location	SNP	SNP in miR sequence	Cancer type	Reference
miR-30c-1	Intron of coding region	rs928508	pre-miRNA	Gastric	(26)
miR-499	Intron of coding region	rs3746444 T>C	Pre-miR-499	Prostate	(27)
miR-26a	Intron of coding region	rs7372209	pri-miR26a-1	OPL	(28)
miR-608	Intron of coding region	rs4919510 C>G	mature-miR	ESCC	(30)
miR-618	Intron of coding region	rs2682818 C>A	pre-miR-618	Lymphoma	(29)
miR-15a~16-1	Intron of ncRNA transcript (DLEU2)	G>C83	pre-miR-16-1	CLL	(32)
let-7/miR-98 cluster	Intron of mlncRNAs units	rs629367	pri-let-7a-2	Gastric	(33)
miR-181	Intron of ncRNA transcript	Rare variant	pre-miR-181b-2	Thyroid	(34)
miR-646	Intron of host gene (AK309218)	rs6513497 T>G rs112880289/ rs6513496	seed stem-loop	HCC	(35)
miR-146a	Exon of ncRNA transcript	rs2910164 G>C	seed/ pre-miR	Gastric	(37)
miR-101-1	Exon of ncRNA transcript	rs578481 rs705509 rs7536540 G>C	pri-miR-101-1	Oral cell	(38)
miR-29b-2	Exon of ncRNA transcript	rs141961287 rs12401619 rs12410786	pri-miR-29b-2	CLL	(32)
miR-371-372-373	Intergenic	rs3859501 C>A	pri-miRNAs	HCC	(41)
miR-196 cluster	Intergenic	rs11614913 C>T	mature-miR	Breast	(42)
miR-125a	Intergenic	rs12976445	pri-miR-125a	Breast	(43)
miRNA-1268a	Intergenic	rs28599926	pre-miR	Astrocytoma	(44)

ies conducted on exonic miRs and their SNPs related to cancer susceptibility is demonstrated in Table 2 (32, 37, 38).

SNPs in intergenic miRNA

The genomic distribution of 1523 human genes revealed that 57.6% of miRs are intergenic. Intergenic miRs are structurally and functionally similar to intronic miRs and have independent transcriptional regulatory elements, such as promoters and terminators. Also, MIR-125a, as an example of intergenic miR (39), contains rs12975333 in the seed region suppresses pri-miRNA processing to pre-miP-125a (40). The list of other instances of intergenic miRs and their studied SNPs is provided in Table 2 (41-44). Generally, these findings imply the changes in primary transcripts, hairpin-shaped precursors (pre-miRs), or mature miRs (with various origins), which may influence the miRNA properties and increase the risk of carcinogenesis. However, more research in future are needed to approve these findings.

Effect of SNPs on miRNAs' regulatory elements in tumors

In addition to the direct effects of SNPs on various sequences of miRs, the SNPs can indirectly affect the regulatory elements involved in a miRs transcription. More than 90% of disease-related SNPs are located in noncoding regions, such as 5'UTRs, which contain important regulatory factors, e.g., promoters and enhancer or components involved in a translation (12). Noncoding SNPs, situated in the regulatory sites of genome include transcription factors, binding sites, and slice sites, which lead to genes misregulation at transcriptional or posttranscriptional level. There are almost more than 20 000 SNPs in human promoters which can moderate the overall level of pri-miRNAs (6). Taken together, variations in Cis or Trans regulatory elements change the miR host genes expression, and subsequently the miRs regulations are embedded in the host gene (45). Table 3 demonstrates some examples of SNP in regulatory elements related to change in transcription factors, binding tendency, and promoter activity (46-49). All these reports confirmed that SNPs in miRs regulatory regions are engaged in miRs processing and finally predisposition to abnormality.

SNPs in coding regions of miRNA's targets and host genes

The gene coding sequences are between 3'/5'UTRs regions. Coding SNPs only come about in the exonic re-

Table 3. Effect of SNP in regulatory element of miRNAs on cancers

miRNA	Location of miRs	SNP	Location of SNP	Cancer type	Reference
miR-148/152 cluster	Intron of coding region	rs4719839	Promoter ~2966bp upper pre-miR	Gastric	(49)
miR-30a	Intron of coding region	rs763354	Enhancer	NSCLC	(46)
miR-122	Exon of ncRNA transcript	rs17669 T/C rs4309483 C>A	upstream regulatory region	HCC	(47)
miR-143/145	Exon of ncRNA transcript	rs41291957 rs353292 rs353293 rs4705341	Promoter	Colorectal	(48)
miR-200b/200a/429 cluster	Intergenic	rs9660710	Promoter Enhancer	NSCLC	(46)

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gions. There are 2 types of coding SNPs: synonymous (sSNPs) and nonsynonymous (nsSNPs). Missense and nonsense are 2 subgroups of nsSNPs. Also, sSNPs can directly affect the translation kinetics and alter the folding pattern and the covalent modification of coded proteins. Also, sSNPs could lead to variation in translation regulation by affecting the mRNA-miRs interaction (50). However, nsSNPs as the most recognized genomic variant, alter the structure of the proteins through amino acid changes and contribute to the molecular function diversity in populations (51).

Effect of coding SNPs on miRNAs' target genes in malignancies

There are about 40% to 60% of miRs binding sites in the coding region of genes (50). miRs binding site on the CDS is related to targets' posttranscriptional regulation and are more effective in translation inhibition . In addition, the synergistic action of miRs-target site in CDS are confirmed in contributing to the recognition of seeds in 3'UTR or in elevating miRNA-mRNA interactions (52). Both SNPs (sSNP and nsSNP) in the coding regions occur frequently and alter the miR regulation (50). A number of SNPs on CDS in target genes were found to create new miR-matching sites (15, 53) or conversely disrupt the binding site (17, 54) (Table 4). As an illustration, nsSNP rs41427445 in CDS of MMP9 create the desired matching in miR-671-3p and miR-657 binding sites and reduced the protein secretion. Also, the missense SNP changes the N38S amino acid and removes the N-glycosylation site (55).

The effect of coding-SNPs in miRNAs' host genes on cancers

SNPs in the coding regions of miRs may alter the expression and maturation of miRs and lead to abnormalities (50). Some examples of SNPs on the CDS in the host genes are presented in Table 4 (49, 56). As a result, coding SNPs in miR's host genes and target genes may alter the processing and binding site on miR-target genes, respectively, and have vital effects on miRs function.

SNPs in miRNAs processing genes

As mentioned earlier, if variants exist in miR-biogenesis genes and genes related to silencing-machinery (AGO family and GEMIN proteins), they can alter the overall silencing efficiency (3). Some of SNPs in miRNAs processing genes are listed in Table 5 (28, 30, 57-60). According to the recent reports, the miR-biogenesis-degradation may interfere with the miR-maturation or even mRNA stability and protein expression due to the SNPs and may have a profound impact on cancer risk.

Conclusion

According to numerous studies, noncoding RNAs act as the main regulators of switching on and silencing the genes in cells, and the gene misexpression is one of the main pillars of the disease-making mechanisms. The emergence of miRs as one of the various noncoding RNAs and their widespread and critical interference in various cell and molecular parts have been considered as an amazing selection of nature in multicellular life. Here, 2 distinct classes of miRs have been reviewed: miRs resulting from intron overlapping with other transcripts and miRs, which are coded from exon transcripts. The new genomic sources of miRs, including transposable elements, pseudogenes, genome duplication, Denovo, and the antisense miRs loci , exhibit the miRs biosynthesis and maturation process and have many unknown dimensions. Despite all the advances made in identifying the biogenesis pathway and activity of miRs, more research is needed. Determining the exact origin of miRs (exon, intron, and

Table 4. Effect of coding SNP on cancers

miRNA	SNP	Location of SNP	Effect of SNP	Cancer type	Reference
mir-196	sSNP (c.313C>T)	Coding region of miR-target gene:(IRGM)	Destroying the miR-196 binding	Crohns	(54)
miR-146a/miR-146b	sSNP (2607G C) rs3733542	Exon of KIT miR-target gene	Changing miR-146a/b binding site	Thyroid	(17)
miR-638	sSNP rs799917 C/T	Exon of BRCA1 miR-target gene	More interaction between BRCA1/miR-638	Breast Gastric	(15) (53)
miR-671-3p miR-657	nsSNP rs41427445/N38S	Exon of MMP-9 miR-target gene	Create miR-binding site	-	(55)
miR-34a	rs72631823 G>A	Coding region of pre-miR-34a	miR-34a down-regulation	osteosarcoma	(56)
miR-148b	nsSNP(missense) rs11170877 A>G	Exon of COPZ1 miR-host gene	changing methionine to Val	Gastric	(49)

Table 5. Effect of SNP in miR- processing genes on cancers

Gene	SNP	Location of SNP	Type of SNP	Cancer type	Reference
GEMIN4	rs7813	Cys1033Arg	nsSNP	ESCC	(30)
	rs3744741	Gln684Arg	nsSNP	Oral	(28)
TRBP	rs784567	Promoter	non-coding	Larynx	(59)
XPO5	rs11077	3'UTR	non-coding	Thyroid	(60)
Dicer	rs3742330	3'UTR	non-coding	OPL	(28)
	rs13078, rs3742330	3'UTR	non-coding	Larynx	(59)
Drosha	rs640831	promoter	non-coding	Lung	(58)
RAN	rs14035	3'UTR	non-coding	Oral	(57)

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intergenic), with respect to specific cell and tissue function of miRs, contributes to recognizing the precise cellular pathways and effective therapeutic interventions with tumor tissues and cells.

SNPs are present in a variety of genomic sequences that are related to miRs directly or indirectly and have a high capability of interfering with the miRs biological activity and controlling various cellular pathways. The phenotype of the cancers occurs during the deregulation of several genes and unusual cell divisions. Since miRs have remarkable effects on cellular processes, their misregulation due to mutation, polymorphism, etc., similar to coding protein genes, will influence the cells pathogenesis pathway. A large number of case-control studies were investigated in this review, most of which indicated the involvement of genetic SNPs in altering the miR expression levels and the miR biogenesis process genes, miR activity, and cancer susceptibility. The fundamental step in the study of association of miRs and tumorigenesis (early stages to metastasis) is identifying the SNPs related to miRs and its involvement in abnormalities. Here, it was aimed to obtain in-depth understanding of how the SNPs work in forming the cellular pathology and recognizing the miRs-controlled pathways. Any change in cancers requires designing a more complex experiments and more precise methods for early diagnosis and even therapeutic purposes. In addition to participating in tumorigenesis through sequential and structural changes, miR polymorphisms act as a double sword in pathogenesis and cancers. Subsequently, miR level deregulation will interfere with the target gene-binding. Based on studies conducted in the field of miR pharmacogenomics, the genetic heredity of miR-SNPs in each person impresses the body's therapeutic response to drugs.

Conflict of Interests

The authors declare that they have no competing interests.

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