

MicroRNAs and PIWI-interacting RNAs in oncology (Review)

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Abstract. RNA molecules that are unable to translate into proteins are classified as non-coding RNA. Non-coding RNA (ncRNA) genes include highly abundant and functionally important RNAs such as transfer RNAs, microRNAs (miRNAs), siRNAs, snRNAs, exRNAs and piRNAs. The number of ncRNAs encoded within the human genome is unknown; however, recent transcriptomic and bioinformatic studies suggest the existence of thousands of ncRNAs. Furthermore, small ncRNAs, including miRNAs and PIWI-interacting RNAs (piRNAs), play an imperative role in the regulation of gene expression of numerous biological and pathological processes. Investigation into the expression and function of small RNA in cancer cells has contributed to gaining a greater understanding of the roles of small RNAs in carcinogenesis. The present review is aimed primarily to discuss the importance of the expression and functions of these small RNAs in carcinogenesis. These studies may provide useful information for future therapies in cancer.

Contents

1. Introduction
2. Functional roles of miRNAs in cancer
3. Oncogenic miRNAs
4. Tumor suppressor miRNAs
5. Deregulation of miRNAs in adrenocortical tumors
6. Deregulation of miRNAs in testicular germ cell tumors
7. Biological roles of PIWI-interacting RNAs (piRNAs)
8. Maternal mRNA decay during maternal-to-zygotic transition
9. piRNAs in cancer
10. Conclusion

1. Introduction

MicroRNAs (miRNAs) have been observed to be deregulated in numerous diseases, including cancer (1). One of the key mechanisms responsible for this miRNA deregulation is the dysfunctional miRNA biogenesis factor (2). In several human cancer types, the deregulated expression of miRNA machinery has been reported. For instance, approximately 60% of ovarian cancer patients show a decreased expression of Dicer and Drosha mRNAs and a low expression of Dicer is correlated with advanced tumor stage (3). Mutations of miRNA processing genes have been observed in human cancers, e.g., *TARBP2* and *exportin-5* in microsatellite unstable colon tumors (4,5), *Dicer1* in pleuropulmonary blastomas (6) and *Drosha* in Wilms' tumors (7). In addition, the conditional deletion of *Dicer1* led to an elevation in tumor development by alteration of the miRNA expression profile in mouse models (8).

Another mechanism underlying deregulated miRNA expression is due to the transcriptional deregulation of miRNA genes. An example is the increased expression of the oncogenic *miR-17-92* cluster by c-Myc (9). In addition to c-Myc, p53 and HIF transcription factors are known to regulate the transcription of a number of miRNA genes (10). Epigenetic changes, such as DNA methylation and histone modifications, potentially affect the transcription of miRNA genes in cancer, e.g., hypermethylation of *miR-337*, *miR-432*, and *miR-371* have been often observed in ovarian cancer (11). The epigenetic silencing of *miR-15a*, *miR-16* and *miR-29b* by histone deacetylases was reported recently in chronic lymphocytic leukemia (CLL) (12).

Another main contributor of miRNA deregulation in cancer is the copy number abnormalities of miRNA genes. One classical example is the deletion of *miR-16* and *miR-15a* at 13q14 in CLL patients, in which approximately 60% of the patients had deletions of these miRNA genes (13). Mutations present within the miRNA genes and RNA editing of the pri- or pre-miRNA transcripts may also affect their processing (14,15).

2. Functional roles of miRNAs in cancer

Cancer is a multistep complex disease, characterized by multiple hallmark traits, as suggested by Hanahan and Weinberg (16). These characteristics include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling the stimulation of angiogenesis, invasion of tissue, metastasis, replicative immortality, deregulation of cellular metabolism, elevation in inflammation, instability in genome and immune

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compromises. In addition, the crosstalk between cancer cells and the tumor microenvironment is necessary to orchestrate these hallmarks (17). It is now clear that miRNAs are involved in all the hallmarks of the cancer phenotypes. miRNAs may therefore function as oncogenic or tumor suppressive miRNAs depending on cellular context.

3. Oncogenic miRNAs

The first identified oncogenic miRNAs belonged to the *miR-17-92* cluster (9). Previous findings have shown the contribution of the deregulation of *miR-17-92* in cancer through multiple pathways, such as metastasis and senescence (18,19). Notably, inhibition of this cluster in cervical cancer led to elevated oncogenic activity of E2F1, suggesting its tumor suppressive activity is dependent on cellular context. Another well-studied oncogenic miRNA is *miR-21*. This miRNA is highly expressed in breast cancer (20), lung cancer (21), glioblastoma (22), adrenocortical and testicular germ cell tumors (23,24). Functionally, *miR-21* is known to regulate multiple tumor suppressor genes, such as *PDCD4*, *PTEN* and *TPM1* (25).

miR-155 is processed from the non-coding RNA (ncRNA) B-cell integration cluster (*BIC*), which is highly expressed in activated B and T cells, and in monocytes/macrophages. This miRNA plays an important role in hematopoiesis and its increased expression is observed in hematological malignancies (26). In addition, high levels of *miR-155* are present in solid tumors, such as breast, prostate, gastric, colon and lung cancers (27,28). *miR-155* is also involved in the regulation of multiple targets involved in different cancer phenotypes, such as *TP53INP1* in apoptosis (29), *VHL* in angiogenesis (30), and *ELK3* in hypoxia (31).

4. Tumor suppressor miRNAs

The first characterized tumor suppressor miRNAs were *miR-16* and *miR-15a* in B-cell CLL. These miRNAs were significantly downregulated in approximately 60% of CLL patients due to the deletion of the 13q14 region where these miRNAs reside (32). Deletion of this locus and a decreased expression of these miRNAs have been reported in other cancer types, such as lung (33) and prostate cancers (34). *miR-15a/16* inhibit cell proliferation and tumor growth by targeting *CCND1* and *CCNE1* (35), and promote apoptosis by targeting the anti-apoptotic factor *BCL2* (36).

5. Deregulation of miRNAs in adrenocortical tumors

Several miRNAs have been observed to be differentially expressed and recognized between malignant and benign adrenocortical tumors. *miR-483-3p* and *miR-483-5p* are consistently overexpressed in adrenocortical carcinoma (ACC) (37). *miR-483* resides within the intron of insulin-like growth factor 2 (*IGF2*), which is overexpressed in approximately 80% of ACC (23). It has been shown that under hypoxic condition, the expression of *miR-210* was induced by HIF1 α , which in turn leads to the suppression of *MNT*, which antagonizes the oncogenic function of MYC (38). Overexpression of *miR-503* was correlated with short overall survival.

On the other hand, a decreased expression of *miR-195* and *miR-497* was consistently reported in several studies (37,39). The overexpression of *miR-195* or *miR-497* suppresses cell proliferation and induces cell death in ACC cells. Of note, *miR-195* and *miR-497* regulate TARBP2 and Dicer in ACC (40).

6. Deregulation of miRNAs in testicular germ cell tumors

A growing number of differentially expressed miRNAs have been identified in testicular germ cell tumors (TGCTs). One of the first characterized oncogenic miRNAs in TGCTs was the *miR-372-373* cluster, which is known to be involved in inducing oncogenic stress, which in turn allow cells to become malignant (41).

miR-199a expression is observed to be decreased in TGCTs, and its putative oncogenic target v-maf musculoaponeurotic fibrosarcoma oncogene family, protein B (*MAFB*) has been identified in TGCTs (42).

7. Biological roles of PIWI-interacting RNAs (piRNAs)

In silkworm, the male phenotype is determined by the presence of two Z chromosomes, whereas the female phenotype is established by having Z and W chromosomes (43). The gender determining region of W chromosome expresses a piRNA precursor, which is processed into gender determining piRNA, termed *fem* piRNA. This piRNA specifically recognizes the masculinization (*Masc*) mRNA and degrades the transcript, suggesting its role in gender determination (43).

During late spermatogenesis, the majority of mRNAs are eliminated in the elongating spermatids; thus, mature sperms retain only few mRNAs (44). It has been recently shown that elimination of these mRNAs in the elongating spermatids requires the activity of MIWI-bound piRNAs, which recruits CAF1 deadenylase complex for their further turnover (44).

8. Maternal mRNA decay during maternal-to-zygotic transition

During maternal-to-zygotic transition, the majority of maternal mRNAs are degraded and replaced by zygotic mRNAs. It has been shown that, in *Drosophila melanogaster*, piRNAs mediate the elimination of maternal *nanos* mRNAs during this transition (45). The degradation of *nanos* mRNA by piRISC is mediated by a similar mechanism as that described above.

9. piRNAs in cancer

The functions of piRNAs and PIWI proteins have started to emerge in human cancers. The deregulated expression of PIWI proteins has been reported in several human tumors, including human seminoma (46), breast, liver, gastric and cervical cancers (47). An increased expression of HIWI is correlated with invasion in cervical cancer and poor prognosis in glioma patients (48).

In addition to the expression of PIWI proteins, deregulated expression of piRNAs has been reported in human cancers, including breast cancer (49), bladder cancer (50), multiple myeloma (51), endometrial cancer (52) and gastric

cancer (53). The functional role of specific piRNAs in human cancer is poorly understood. Only *piR-823* is currently known to regulate *de novo* DNA methylation and angiogenesis in multiple myeloma (51).

10. Conclusion

The abovementioned studies indicate that investigations focus on exploration of the importance of ncRNAs in cancer. These studies are likely to result in better treatment strategies based on these ncRNA interactions in future.

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