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Minireview

Beyond HPV: Oncomirs as new players in cervical cancer

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Abstract MicroRNAs (miRNAs) are a recently discovered family of 18–24 nucleotide non-coding RNAs that can negatively regulate target mRNAs. All studied multicellular eukaryotes utilize miRNAs to regulate basic cellular functions including proliferation, differentiation, and death. It is now apparent that abnormal miRNA expression is a common feature of human malignancies. This review discusses the various cancer-relevant miRNAs (oncomirs) especially in cervical tumorigenesis and the potential role of oncomirs as therapeutic agents and targets for the treatment of cervical cancer.

Keywords: MicroRNA; Oncomirs; Cervical cancer; Apoptosis; Tumor suppressor

1. Introduction

MicroRNAs or miRNAs, initially discovered in the early 1990s as small, non-coding RNA molecules able to regulate expression of key genes involved in development, have now been associated with the regulation of diverse physiological processes including cell differentiation and cell division [1]. Over 500 human miRNA molecules have been identified so far. In 1993, Rosalinda et al. discovered the first microRNA (miRNA) named *lin-4* and the term introduced for the first time in a set of three articles that appeared in the October 2001 issue of *Science*. It is known that miRNAs are highly conserved molecules; for example, the complete mature miRNA sequence of *let-7*, isolated the first time in *Caenorhabditis elegans*, has been evolutionarily conserved from worms to humans. Thousands of miRNAs have been identified in nematodes, insects, birds, amphibians, fishes, plants, mammals, and even viruses using molecular cloning and bioinformatics prediction strategies [2–4]. Bioinformatics approaches have proved to be very useful toward this goal in guiding the experimental investigation. Computer-based prediction approaches of miRNAs and their targets, and biological validation techniques for ascertaining these predictions, currently play a central role in the discovery of miRNAs and in elucidating their function [5,6].

A number of microRNAs, encoded in the human genome have been shown to be intrinsically involved in cancer pathogenesis and progression. There is sufficient evidence that some of these ''oncomirs'', as these cancer-associated miRNAs are sometimes referred to, possess a tumor-suppressive/pro-apoptotic role while others have anti-apoptotic/proliferation promoting roles in the cell [7]. It has also been reported that key miRNAs have regulatory roles in inflammation and metastasis [8]. A number of recent studies have reported miRNA dysregulation in various forms of cancer. Abnormalities in miRNA expression have been implicated in several forms of solid tumors such as cervical [9], breast [10], colorectal [11], lung [12] and also in at least two forms of leukemia [13]. Fundamental relationships exist between the pathogenesis of cancer and miRNA dysregulation, as demonstrated in a large, recent study, where a set of 127 mammalian microRNAs were expression profiled across a vast panel of clinical samples [14]. This study strongly suggested that the ''developmental history of a tumor is reflected in its miRNA expression patterns''. A recent study proved the involvement of a new class of non-coding RNAs (ncRNAs), named ultra conserved genes, in human cancers and found that miRNAs can directly target and regulate the expression of these ncRNAs [15]. Among the first clues for their involvement in cancers was the observation that miRNAs are frequently located in cancer-associated genomic regions, which include minimal regions of amplification, loss of heterozygosity, fragile sites, and common breakpoint regions in or near oncogenes or tumor suppressor genes [16]. The discovery of the involvement of microRNAs in the initiation and progression of human cancer may provide additional targets for anticancer treatment design.

2. Cervical cancer

Cervical cancer is one of the most common cancers in women worldwide, with an estimated global incidence of 470000 new cases and approximately 233000 deaths per year [17,18]. Cervical cancer is the leading cause of death from cancer in many low resource countries where widespread screening by cervical cytology is still unavailable. The incidence is lower in developed countries as a consequence of cervical screening and of ongoing active health education programs. The causal relationship between high-risk HPV (HR-HPV) infection and cervical cancer has been well documented in epidemiological

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Abbreviations: miRNAs, microRNAs; HPV, human papillomavirus; og, oncogenic; tsg, tumor suppressor gene; EBV, Epstein-Barr virus; KSHV, Kaposi sarcoma-associated herpesvirus; HSV, Herpes Simplex Virus; SV40, Simian virus 40

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and functional studies. High-risk HPVs, such as HPV16, HPV18, and HPV31, have been detected in up to 99.7% of cervical squamous cell carcinomas and 94–100% of cervical adeno- and adenosquamous carcinomas [19,20]. The high-risk HPV oncoproteins, E6 and E7, contribute to cervical carcinogenesis by inactivating the cellular tumor suppressor proteins p53 and pRb, respectively [21–23].

Many authors have reported that each cancer tissue has a specific microRNA signature and microRNA based cancer classification is a very effective and potential tool [14]. It is interesting to speculate that the variations in miRNA expression in cervical cancer cell lines contribute to deregulation of the cell cycle regulatory pathway in cervical cancer. Thus miRNA expression patterns may serve as potential biomarkers of pre-invasive cervical disease and potential therapeutic targets. There are currently no drugs in the clinic that specifically target HPV and the need to discover more effective and more specific inhibitors of such key molecular targets is clearly justified.

3. MiRNA expression profile in cervical cancer cell lines

Wang et al. found that of 174 miRNAs (including the novel miR-193c) which could be grouped into 46 different miRNA species, miR-21, miR-24, miR-27a, and miR-205 were most abundant in cervical cancer- or cervical intraepithelial neoplasia-derived cell lines [24]. There was however no correlation observed between their expression with the presence or absence of an integrated or episomal HPV genome. All cell lines examined contained no detectable miR-143 and miR-145. HPV-infected cell lines expressed a different set of miRNAs when grown in organotypic raft cultures as compared to monolayer cell culture, including expression of miR- 143 and miR-145. Suggesting a correlation between miRNA expression and tissue differentiation. miRNA array analyses for age-matched normal cervix and cervical cancer tissues, in combination with Northern blot verification identified deregulated miRNAs in cervical cancer tissues. Downregulation of with miR-126, miR-143, and miR-145, miR-218, and miR-424 (Table 2) and upregulation of miR-15b, miR-16, miR-146a, and miR-155 (Table 1). Functional studies showed that both miR-143 and miR-145 are suppressive to cell growth. When introduced into cell lines, miR-146a was found to promote cell proliferation. The authors hypothesized that downregulation of miR-143 and miR-145 and upregulation of miR-146a play a role in cervical carcinogenesis [24].

Table 1
MicroRNAs overexpressed in cervical cancer cell lines.

miRNA	Chromosome	Putative function
hsa-miR-210	11	Oncogenic
hsa-miR-182	07	og/tsg
hsa-miR-183	08	og/tsg
hsa-miR-200c	12	Tumor suppressor
hsa-miR-203	14	og/tsg
hsa-miR-193b	16	Oncogenic
hsa-miR-34a	01	og/tsg
hsa-miR-31	11	og/tsg
hsa-miR-210	11	og/tsg
hsa-miR-27a	19	og/tsg
hsa-miR-503	X	og/tsg
hsa-miR-27b	09	og/tsg
hsa-miR-199a	19	og/tsg
hsa-miR-199b	09	og/tsg
hsa-miR-145	05	og/tsg
hsa-miR-133a	18	og/tsg
hsa-miR-133b	06	og/tsg
hsa-miR-214	01	og/tsg
hsa-miR-127	14	og/tsg

Table 2
MicroRNAs underexpressed in cervical cancer cell lines.

miRNA	Chromosome	Putative function
hsa-miR-126	09	og/tsg
hsa-miR-145	05	og/tsg
hsa-miR-451	17	og/tsg
hsa-miR-195	19	og/tsg
hsa-miR-143	05	og/tsg
hsa-miR-199b	09	og/tsg
hsa-miR-1	01	og/tsg
hsa-miR-495	14	og/tsg
hsa-miR-497	17	og/tsg
hsa-miR-133b	06	og/tsg
hsa-miR-223	X	og/tsg
hsa-miR-146a	05	og/tsg
hsa-miR-126-AS	09	og/tsg
hsa-miR-150	19	og/tsg
hsa-miR-376a	14	og/tsg
hsa-miR-214	01	og/tsg
hsa-miR-487b	14	og/tsg
hsa-miR-10b	02	og/tsg
hsa-miR-218	04	og/tsg
hsa-miR-149	02	og/tsg
hsa-miR-203	14	og/tsg

Downregulation of miR-143 and miR-145 has been found in several other cancers, including colorectal cancer [25], B-cell lymphoma [26], and recently in cervical cancer [27,28]. Thus, finding is important for understanding mechanisms by which miR-143 and miR-145 are involved in carcinogenesis. Various studies show that miR-46a is a NF-kappaB-dependent gene [29–31]. Expression of miR-146a appears to vary in different cancer tissues. Increased level of miR-146a was observed in Burkitts' lymphoma lines with EBV-LMP1 expression [30,32], but decreased levels seen in hormone-refractory prostate cancer [31] and papillary thyroid carcinoma [33]. The authors concluded that upregulation of miR-146a expression in cervical cancer is beneficial for cancer growth since introduction of miR-146a into cancer cells increased cell doubling time and promoted cell proliferation. Moreover, Wang et al. were unable to identify a single HPV16-derived miRNA from HPV16 + CaSki cells, although other nuclear DNA viruses do encode miRNAs [34], including EBV [35]; KSHV [36–38]; HSV-1 [39,40]; and SV40 [41]. Recent reports have suggested that miRNAs contribute to a variety of cell functions and are involved in the development of human cancers [42]. miRNAs have been also characterized recently as potential oncogenes that promote the development of human B-cell lymphoma (miR-17-92 cluster) [43] and the proliferation and tumorigenesis of primary human cells (miR-372 and miR-373) by neutralizing p53-mediated CDK inhibition [44]. Another study suggested that overexpression of miR-17-5p, miR-20a, miR-21, miR-92, miR-106a, and miR-155 could be considered an miRNA signature of solid tumors [45]. Eighteen miRNAs were upregulated where 15 were downregulated in cervical cancer tissues. The increased expression of miR-15b, miR-16, miR-146a, miR-155, and miR-223 observed in cervi-

cal cancer tissues has also been implicated in the development of other human cancers: miR-15 and miR-16 regulate apoptosis by targeting BCL2 [46] and their mutation has been associated with chronic lymphocytic leukemia [47]; miR-16 is also involved in control of cytokine RNA instability [48]; miR-146b levels are highly increased in papillary thyroid carcinoma [33]; miR-155 has recently been implicated in the development of lymphoblastic leukemia/high-grade lymphoma [49] and lung cancer [50] and in the regulation of human fibroblast angiotensin II type 1 receptor expression [51]; miR-223, along with the transcription factors C/EBPa and NFI-A, participates in regulation of granulocytic differentiation by suppressing the transcription of NFI-A mRNA [52].

4. Altered miRNA expression in cervical carcinomas

Lee et al. identified altered miRNA expression in early stage ISCCs and normal epithelial tissues of the cervix. The findings suggest that miR-127 may be a marker for lymph node metastasis of ISCCs and that miR-199a may be a potential therapeutic target for cervical cancer therapy [9]. Tissue-specific patterns of miRNA expression have been recently reported; they are thought to reflect embryologic development [53]. Several reports showed that specific overexpression or underexpression of miRNAs differ according to the particular tumor types [43]. Most human miRNAs are found between protein-coding genes; approximately one-third are located within the introns of annotated mRNAs. These intronic miRNAs are usually in the same orientation as the pre-mRNA, and thus, could be under the control of the promoter driving the primary mRNA transcript [54]. Despite the uncertainty regarding the functional effects of miRNAs, the miRNA expression profile may be used as a prognostic marker for clinical aggressiveness of human cancer. One such example is chronic lymphocytic leukemia. Calin et al. reported a miRNA expression signature composed of 13 mature miRNAs that were associated with prognostic factors and disease progression [55]. Recently, a study on pancreatic endocrine and acinar tumors revealed that the overexpression of miR-21 is strongly associated with both a high Ki67 proliferation index and the presence of liver metastasis [56]. The expression of miR-127 was significantly higher in the group of ISCCs with lymph node metastasis than in those without metastasis. In addition, there were two major classes of early stage ISCC, identified by hierarchical clustering, which showed differences in lymph node metastasis. Rather, loss- or gain-of-function of specific miRNAs seems to be a key event in the genesis of a variety of cancers. Therefore, miRNAs might be potential targets for therapy. This finding points toward miRNAs as tumor suppressors and highlights their potential as a new kind of regenerative medicine to treat cancer.

5. Conclusion and future directions

It has been less than 8 years since the discovery of the first miRNAs, and it is likely that many others await discovery. The in vivo study provides an exciting step towards miRNA therapy, and the potential for designing molecular leads based on the modulation of miRNAs seems good. The effects of the antagomirs on the protein level, however, were only examined for a few enzymes connected with cholesterol metabolism [57]. The efficient development and delivery of sufficient amount of antagomir into the proper target cell without overt toxicity requires fine tuning of molecular technology before it can be tried clinically. In addition, unwanted side effects to such therapeutic agents may occur over the long term. As miRNA-based therapies begin to be evaluated in clinical studies, the next few years will test the promise of relevant drugs, allowing us to combine the specificity of siRNA and the mismatch tolerance of miRNA. Still although studies of oncomirs are at its dawn, a new era of anticancer treatment with these natural molecules can be forecast, bringing new insights in neoplastic disease and new promising therapeutic strategies.

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