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REVIEW

Dysregulation of microRNA Expression in Human Cervical Preneoplastic and Neoplastic Lesions

Ádám Galamb · Márta Benczik · Balázs Zinner · Eszter Vígh · Kornélia Baghy · Csaba Jeney · András Kiss · Gábor Lendvai · Gábor Sobel

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Abstract Data discussed in recent reviews demonstrated that dysregulation of microRNA (miRNA) expression profiles occurs during cervical carcinogenesis and characteristic up- or downregulation of certain miRNAs might be used as biomarkers. The majority of altered miRNAs, however were found to be inconsistent upon comparison with cancerous and normal cervical epithelia in the discussed studies due to several reasons. The results obtained in this present review suggest the need for further investigations on miRNAs on larger sample sizes in order to indicate sensitivity and specificity by means of well defined, "unified" methods. In addition, obtaining further data on the clinical course and outcome of patients in comparison to the dysregulation of miRNA expression profile could turn miRNAs into prognostic and/or progression markers. Inhibition of overexpressed miRNAs, as suggested by some authors, might even serve as target for cancer therapy.

Keywords Cervix · Cervical cancer · microRNA · Biomarker · Screening

Ádám Galamb, Márta Benczik, Gábor Lendvai and Gábor Sobel equally contributed

Á. Galamb · B. Zinner · G. Sobel (✉)
2nd Department of Obstetrics and Gynecology, Semmelweis University, Üllői út 78/a, 1082 Budapest, Hungary
e-mail: sobelg@gmail.com

M. Benczik · C. Jeney
Cellcall Kft, Röppentyű u. 48, 1134 Budapest, Hungary

E. Vígh · A. Kiss · G. Lendvai
2nd Department of Pathology, Semmelweis University, Üllői út 93, 1091 Budapest, Hungary

K. Baghy
First Institute of Pathology and Experimental Cancer Research, Semmelweis University, Üllői út 26, 1085 Budapest, Hungary

Introduction

Cervical cancer is the third most common malignant tumor among women worldwide, responsible for 529 800 cases yearly and 275 100 cancer-related deaths in 2008 [1, 2]. There are, however, significant geographical differences around the world in cervical cancer incidence and mortality, with more than 85 % of cases occurring in developing countries [1, 2]. Introduction of the "Pap" test for cervical cancer screening resulted in a significant reduction of both cancer incidence and mortality [3]. Moreover, early cancer detection was further supported by new evaluation methods, especially the guideline summarized at the Bethesda Conference in 2001 [4], as well as by the etiological role of the human papilloma virus (HPV), discovered by Harald zur Hausen and his group, in cervical carcinogenesis [5].

More recently, cytology as a gold standard has been criticized, since while the high specificity of this method is accepted, its relatively low sensitivity is a problem [6]. According to a recent study by Ronco et al., the more extensive use of modern molecular biological methods, first of all HPV DNA testing, led to a 60–70 % reduction in invasive cervical cancer incidence as compared with cytology-based screening [7].

Detection of high risk HPV (hrHPV) infection, however does not provide answers to whether the infection is of the productive, transient or of the transforming type [5, 7–10]. Several novel biomarkers have been developed for detection of transformed, neoplastic cells, with the goal to increase the sensitivity and/or specificity of cervical cancer screening tests, even in combination with cytology and/or HPV DNA testing (for review see [9, 11]. Some of these biomarkers might even have the potential to become prognostic markers [12, 13].

Besides HPV DNA, the newly introduced biomarkers are also capable of detecting other viral components, such as HPV RNA, HPV oncoproteins (E6/E7) or overexpressed cellular

genes, RNAs and/or proteins involved in cervical carcinogenesis [8, 9] .

Several studies proved the correlation between microRNA (miRNA) expression and carcinogenesis including premalignant cervical lesions, preinvasive and invasive cervical cancer [14–21]. Some of the miRNAs, which become altered in cervical cancer were suggested to be useful biomarkers in diagnostics or even suggested as possible prognostic markers and targets for therapy [13]. In the followings, recent progress in the field of miRNA research will be presented with focus on the potential of miRNA expression profiles as diagnostic, prognostic markers and potential targets for therapy in cervical carcinogenesis.

miRNAs

miRNAs are small (18–25 nucleotides in size) endogenous non-coding RNA molecules, which regulate gene expression at posttranscriptional level by affecting messenger RNAs (mRNA) by means of translational suppression (Fig. 1a–d). Since partial complementer binding of miRNA is sufficient for the regulation effect much effort has been made to reveal the potential ways a miRNA is able to bind to mRNA [22], indicating an unsurpassed help in target prediction of miRNAs (Fig. 1b and c). Over 1000 human miRNAs have been identified since the first one discovered in 1993; at the time named lin-4 [23], later identified by the term miRNAs [24, 25]. Shortly after their discovery, data saw light suggesting that miRNAs are involved in carcinogenesis [26] referred to as "oncomirs" by some authors [15]. It was verified that miRNAs might function as either oncogenes or tumor suppressors depending on the cell/tissue types (Fig.1d) [15, 27, 28]. Studies demonstrated that miRNAs are dysregulated in cancer and the changes in expression profiles might classify human malignancies and even predict the outcome [12, 26, 27, 29]. This means that each cancer has a specific miRNA profile or pattern [26], which reflects both the tissue of origin and the stage of carcinogenesis [15, 27, 29–32]. The mechnism of miRNA deregulation, however, is not exactly clear, there are several biogenesis machineries contributing to the alteration [18, 27]. Both up- and downregulation of different miRNAs were reported in different types of cancer [27, 28].

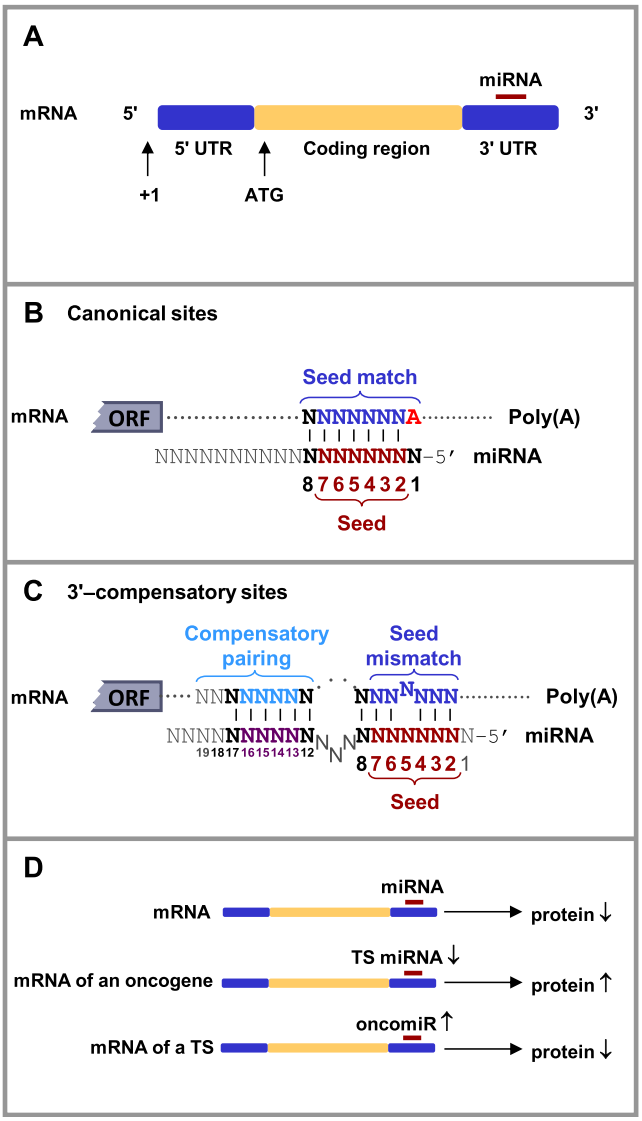

Fig. 1 miRNAs interfere with gene expression at posttranscriptional level. **a** Regulation role of a miRNA is attained by binding to 3′-UTR (untranslated region) of target mRNA. **b** Partially complementer binding is sufficient, which involves the nucleotides 2–7 (6mer), 1–7 (7mer-A1), 2–8 (7mer-m8) or 1–8 (8mer) of 5′ end of miRNA called the "seed". These are considered to be the main basepairing types. **c** A mismatch in the seed region can be compensated by a ≥4–5 nucleotide pairing located 1–5 nucleotide farther from the seed. However, this type tends to be only slightly more effective than the canonical binding types. **d** Interfering of miRNA with gene expression results in translational arrest of mRNA and reduced protein production. In diseases, mainly in cancers, the production of an oncogene can be increased if the regulatory miRNA(s) (called tumor suppressor miRNA) is/are downregulated; whereas a tumor suppressor protein may be eliminated if the regulatory miRNA(s) (called oncomir) is/are upregulated. *mRNA* Messenger RNA, *UTR* Untranslated region, *ATG* Start codon, *miRNA* microRNA, *ORF* Open reading frame, *TS* Tumor suppressor (gene)

miRNA Expression Profiles in the Normal Cervix and in Preneoplastic and Invasive Cancerous Lesions

miRNA expression profiles were characterized in human cervical cancer cell lines and normal cervical tissues [20] followed by several studies in cervical cancer, which demonstrated that miRNA expression profiles are different in the normal and cancerous cervix. The majority of these studies compared miRNA expression profiles in cervical cancer with their normal – usually matched - cervical tissue

counterparts [16, 19, 20]. The results of these studies, however are inconsistent [31, 33].

High variability of miRNA expression was observed in 4 cervical squamous cell carcinomas, 5 high-grade (HSIL) and 9 low-grade (LSIL) squamous intraepithelial lesions, as compared with 19 normal cervical tissues [16]. It was shown that high "natural expression variability exists among human samples", however, aberrant miRNA expression was present in the studied cancerous and preneoplastic lesions [16]. The samples could not be separated from each other based on miRNA pattern, probably due to the previously mentioned high varability. The authors of this particular study suggested that the "variability" might be associated with the fact that some of the normal cervical samples were infected with HPV, which might influence miRNA expression, or that natural genetic variations, aging and other health problems are linked to the variability [16].

It was demonstrated that some miRNAs are upregulated (as miRs −21, −27a, 34a, −155, 182, −196a, −199, −221), while others are downregulated (as miRs −143, −145, −99a, −26a, −203, 218–497 etc.) in different stages of cervical carcinogenesis [13, 15–17, 20, 21, 31, 34–36] (Table 1). Certain authors have found the downregulated miRNAs to be downregulated in other cancers, too, such as miRs −143, −145 in colorectal cancer [37], miR-199a in hepatocellular carcinoma [38]. Others, however, have reported on contradictory data, according to which increase rather than decrease of miRNA expression was detected in invasive cervical carcinoma when compared with normal cervical tissue [19].

miRNA expression was analysed comparing normal cervix and preneoplastic cervical lesions [16]. Interestingly some miRNAs were downregulated in preneoplastic lesions as compared to normal tissues, but upregulated in cancer [16].

Several miRNAs were found to be upregulated in preneoplastic lesions, such as miRs −148a, −302b, −10a, −196 and −132 [16]. Interestingly, known oncogenes (as myc, kRAS etc.), tumor suppressors (TP53, PTEN) were found to be specific targets of the aberrantly expressed miRNAs [16]. It was found that miR-92 is highly expressed in cervical cancer as compared with normal cervical tissue [39].

Lee et al. [19] in a study of 10 cases each of advanced invasive cervical cancer and normal cervix found that miR-127 is a marker for lymph node metastasis of invasive cervical cancer and suggested that miRNA profiling might be used as a prognostic marker for "clinical aggressiveness". In another study on 102 cervical cancer cases miR-200a and miR-9 were found to probably influence metastasis of cervical cancer cells and to likely predict survival of the patients [12]. These authors suggested a "miRNA-based model to predict cervical cancer survival" [12]. Luo et al. [13] analysed 60 cervical cancer tissues and corresponding non-tumorous epithelia for the expression of miR-497. They found that miR-497 was

Table 1 Altered expression of miRNAs in premalignant and malignant cervical lesions

a. Increased expression of miRNAs	References
let-7f	[43]
miR-7	[17]
miR-9	[19, 43]
miR-10a	[16, 21]
miR-15b	[21]
miR-16	[21, 41, 43]
miR-17	[43]
miR-18a	[17]
miR-20a,b	[17, 21, 41]
miR-21	[12, 20, 21, 33, 41, 43]
miR-24	[21]
miR-27a	[43]
miR-31	[17, 43]
miR-34a	[43]
miR-92	[39]
miR-93	[17, 21, 41]
miR-106a	[21, 41]
miR-127	[19, 43]
miR-132	[21]
miR-133a,b	[19, 43]
miR-141	[17]
miR-142	[17]
miR-145	[19]
miR-146a	[17, 21]
miR-148a	[21]
miR-155	[21, 41]
miR-181c	[21]
miR-182	[21, 31, 41]
miR-183	[21, 31, 41]
miR-185	[21, 41]
miR-193	[43]
miR-196a	[21]
miR-199	[19, 43]
miR-200	[17, 43]
miR-203	[12, 16]
miR-205	[21, 43]
miR-210	[17, 43]
miR-214	[19, 43]
miR-223	[21]
miR-224	[17, 21, 41]
miR-302	[21]
miR-324	[21]
miR-429	[17]
b. Decreased expression of miRNAs	References
miR-1	[17]
let-7b, c	[21, 36, 44]
miR-10b	[17, 21, 44]
miR-26a	[16, 21]
miR-29a	[16, 21, 41]

Table 1 (continued)

miR-30b	[21]
miR-34a	[21, 41]
miR-99a,b	[16, 17, 21, 31]
miR-100	[17, 21, 41, 44]
miR-125a,b	[21, 41, 44]
miR-126	[21, 41]
miR-127	[17, 21, 41]
miR-133a,b	[21]
miR-140	[17]
miR-142	[31]
miR-143	[16, 17, 20, 21, 31, 36, 44]
miR-145	[16, 17, 21, 36, 41, 44]
miR-149	[19, 36]
miR-150	[31]
miR-152	[17]
miR-195	[17, 31]
miR-196b	[36]
miR-199a,b	[16, 21, 31, 44]
miR-203	[12, 16, 19, 21, 36]
miR-211	[31]
miR-214	[17]
miR-218	[12, 17, 21, 41, 42]
miR-223	[31]
miR-320	[17]
miR-328	[31]
miR-368	[17]
miR-376	[17]
miR-378	[21]
miR-422a	[21]
miR-424	[21]
miR-450	[21]
miR-455	[21]
miR-497	[13, 17]
miR-513	[16, 21]
miR-574	[21]

downregulated in the cancerous tissue and correlated closely with FIGO Federation International of Gynecologists and Obstetrics) stage and lymph node metastasis in cervical cancer patients [13].

Rao et al. [17] studied 13 HPV-16 or −18 infected patients with cervical cancer. A total of 18 miRNAs were upregulated, 19 miRNAs were downregulated out of 924 miRNAs, as compared with the normal adjacent cervical tissue. They concluded, however, that miRNA expression was not associated with lymph node or vascular invasion and histological differentiation of the cancerous tissue, and also that the expression was independent of cancer stage and metastasis [17].

HPV and miRNA Expression Profile

After discovery of the association between HPV infection and cervical cancer major progress was made by learning how the binding of HPV oncoproteins E6 and E7 results in degradation of tumor suppressor proteins p53 and pRb and leads to cervical cancer [40].

Wang et al. [21] demonstrated aberrant expression of several miRNAs in association with HPV infection. Decreased p53 expression increased miR-200c expression resulting deactivated SLIT2 – a "candidate tumor suppressor gene" – expression, which resulted the development of cervical carcinoma. Other studies did not find different expressions of miR-9 and miR-200a between normal and cancerous cervical tissue [21, 41]. Li et al. [41] analysing 78 samples, demonstrated that reduced miR-218 expression was associated with hrHPV infection and according to their opinion down-regulation of miR-218 has a role in development of cervical carcinogenesis.

Based on microarray and/or quantitative real-time PCR analysis, Martinez et al. [42] showed that 3 miRNAs were overexpressed, 24 were underexpressed in cervical cell lines with integrated HPV-16 DNA. miR-218 was "specifically underexpressed" in HPV containing cell lines and cervical carcinoma tissue and was associated with the E6 oncogene of HPV-16. More recently "progressive miRNA profiles" were demonstrated during cervical carcinogenesis with increased expression of 12 and decrease expression of 9 miRNAs [41].

It was shown that HPV E6 regulates the expression of miR-23b, miR-34a, miR-218 and HPV E7 of miR-15a/-16-1, −203 [28]. On the other hand, it was demonstrated that cellular miRNAs might regulate HPV viral gene expression [28]. Yu et al. [39] detected high expression of miR-92 in 34 cervical cancers compared with 34 normal cervical samples. They found that HPV 16 E6 upregulates miR-92 expression in cervical cancer cell lines in association with the decrease of tumor suppressor phosphatase and tensin homologue (PTEN) protein expression [39].

Conclusions

A large number of studies have analysed the expression profile of miRNA in premalignant and malignant cervical squamous epithelial lesions in comparison with normal cervical squamous epithelia. The results, the identified up- or down-regulation of certain miRNAs, are quite inconsistent upon comparison of the discussed studies. This might be due to the way the samples were collected (fresh, frozen, paraffin embedded), the mode of cell isolation (macro-, microdissection or no dissection), the HPV status of normal and neoplastic samples used, the available clinical data, the application of in vitro or in vivo models as cell lines, xenographs etc.). All data agree, however, that significant dysregulation of miRNA expression profiles occurs during cervical carcinogenesis and certain miRNAs act as oncogens, while others as tumor suppressors. Some of the up- or downregulated miRNAs may be so characteristic that they might be used as biomarkers. For this, however, studies should be performed on larger sample sizes to indicate sensitivity and specificity using well defined,

"unified" methods. In addition, obtaining further data on the clinical course and outcome of patients in comparison to the dysregulation of miRNA expression profile could turn miRNAs into prognostic and/or progression markers. Inhibition of overexpressed miRNAs, as suggested by some authors, might even serve as target for cancer therapy.

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