The role of microRNA (miRNA) as a biomarker in HPV and EBV-related cancers

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Abstract

Introduction and objective. Biomarkers are measurable biological indicators of many disease states. Particularly noteworthy are short nucleotide sequences involved in the regulation of many cellular processes. Their level in body fluids constitutes an important biological marker of serious diseases, such as cancer or cardiovascular diseases. For example, different types of microRNA may be used as biomarker in virus-associated cancers. The aim of this article was to review the current knowledge on the miRNAs and their role in viral-related cancers (EBV and HPV). The article reviews information available in journals and on electronic databases.

Brief description of the state of knowledge. A significant part of the world’s population hosts at least one of the oncoviruses, but only a small percentage of them undergo a cancerogenesis to which these infectious agents contribute. Interaction between the host cell and viral factors can lead to the origination of a microenvironment favourable to oncogenesis. Cancer arises as a result of dysregulation in many cellular processes, and particularly important are short RNA sequences which regulate the processes that can cause this disease. The varied expression of this ribonucleic acid contributes to many diseases and provides valuable information about health. Importantly, these molecules are differentially expressed in virally-induced cancer. Many publications have confirmed the relationship between the expression of specific types of miRNA and cancers associated with EBV and HPV.

Conclusions. The use of miRNAs as biomarkers of neoplastic diseases associated with EBV and HPV infections may significantly contribute to the reduction of mortality caused by these viruses, and thanks to the development of modern technologies they are an attractive research object.

Key words

cancer, biomarkers, microRNA, HPV, EBV

INTRODUCTION AND OBJECTIVE

Many biological markers have been applied in cancer diagnosis, therapy or monitoring. Currently, the biomarkers of cancer are mainly proteins present in fluids and tissues, for example, alpha fetoprotein (AFP) and carcinoembryonic antigen (CEA) [1]. Over the past 20 years, a group of small regulatory RNA molecules has aroused great interest and the correlation between expression levels and specific neoplasms has made microRNAs a popular research subject. Moreover, their use as a biological marker may prove to be a breakthrough in terms of diagnostics at all stages of cancer [2–4]. The presence of these molecules in body fluids, such as blood and urine, in addition to transmitting signals to other types of cells, makes them an excellent source of information about the state of the cell [5, 6].

STATE OF KNOWLEDGE

MiRNA – characteristics. Short nucleotide sequences called microRNAs were discovered in the nematode Caenorhabditis elegans, where this non-coding RNA was responsible for binding lin-14 mRNA, which resulted in inhibition of LIN-14 protein synthesis [7–9]. Reinhart et al. [10] reported the presence of miRNAs in Arabidopsis, confirming that this type of RNA appeared in the common ancestor of plants and animals. It is concluded that miRNAs can make up about 1% of all genes in mammals and control about half of the genes encoding human proteins [4, 11, 12]. MiRNA precursors are most common in the regions between genes and introns which were previously called ‘junk DNA’ because their function was unknown. About 98% of human DNA is untranslated and therefore not convert into a protein product. The ENCODE project found that more than 80% of the human genome is biologically active, and it is known that some ‘junk DNA’ is transcribed into non-coding RNA [2, 13]. The active and mature miRNA exists in the form of single-stranded RNA associated with the Argonaute family of proteins and forms the fundamental component of RISC (microRNA induced silencing complex). This complex binds to a specific mRNA, usually in the 3’untranslated region, leading to miRNA degradation or translation inhibition. In some cases, the miRNA-Argonaute complex can increase gene expression [14, 15]. This type of RNA is a fundamental regulator of cellular processes, such as proliferation, differentiation or apoptosis. The expression of this single-stranded molecule varies according to organs and cell types. Both positive and negative regulation of mRNA can cause serious disease, and it should be noted that hundreds of miRNAs are associated with human disease [2, 16, 17], which include cancer, cardiovascular diseases and diseases related to the immune system [15, 18, 19].
The currently used biomarkers often do not show sufficiently high sensitivity and specificity. Detection of protein biomarkers is difficult due to the complexity of their structure and the problem of finding accurate detection methods [20]. Therefore, new precise cancer indicators are constantly being searched for. Both DNA and miRNA biomarkers showed increased storage time and appropriate quality [21] and, moreover, the development of new tests requires less time and less cost compared to protein biomarkers. MiRNA levels can be measured using sensitive techniques, including Polymerase Chain Reaction (PCR) or Next Generation Sequencing (NGS), which are constantly being improved. The immunossaay method also deserves special attention in the determination of miRNA because its advantages include high analytical specificity and short waiting time for results [22]. This technique has been used successfully, for example, in the determination of miRNAs in colorectal tumour and surgical margin tissue samples [23]. It should be added that miRNA is stable to most RNA degradation conditions, such as very low or high pH [4, 24, 25]. Importantly, the combination of different miRNAs with other biomarkers could be used in the future for precise cancer diagnosis, for example, miR-29a and miR-335 in combination with matrix metalloprotease protein-2 (MMP-2) showed better diagnostic efficacy than CEA and tumour antigen 15–3 (CA 15–3) assays used in breast cancer [26]. As a result, miRNAs have wide potential as a biomarker in diagnostics, prognosis and anti-cancer therapy [4, 24, 25].

MiRNAs and cancer. Cancer is a serious problem for human health worldwide, and constitutes the second most common cause of death, which arises through multiple mutations in genes that stimulate the cell to divide continuously and indefinitely [3]. GLOBOCAN estimates the number of new cancer cases at approximately 19 million, and nearly 10 million deaths in 2020 [27]. The pathogenesis of neoplastic diseases results from disturbed intercellular relations as well as dysfunction of important genes, such as tumour suppressors [3]. The role of miRNA in the development of cancer was studied by Calin et al. [28] on CLL (chronic lymphocytic leukemia). It was then noted that the region of the chromosome that is frequently deleted in CLL lacked the tumour suppressor gene, and instead two microRNA genes were discovered: miR-15a and miR-16–1. Deletion of these two miRNAs increased the proliferation of human and murine B cells by modulating the expression of genes that control cell cycle progression [29]. Moreover, the miR-15/16 cluster has been shown to act as a tumour suppressor which targets the BCL2 oncogene [30]. In 2004, Calin et al. mapped all known microRNA genes and found that many of them reside in regions of the genome involved in chromosomal changes, such as deletion or amplification in a wide variety of human tumours [31]. This non-coding RNA may act as oncogenes or tumour suppressors, and it has been proven that a large proportion of them are involved in chromosomal changes in human cancer.

Analysis of miRNA enables the differentiation between normal and cancer tissue. In addition, it allows distinguishing a specific type of cancer and predicting disease outcome or response to therapy [31]. Deregulation of miRNAs in the tumour can occur as a result of epigenetic changes, including modification of histones or abnormal DNA methylation [32], for example, Saito et al. [33] showed that the use of a DNA methylation inhibitor and a histone deacetylase inhibitor restored expression of miR-127, which targets the BCL6 oncogene. Methylation of specific miRNA genes has downstream cellular consequences. For instance, methylation of the miR-345 gene in colon cancer is associated with inhibition of apoptosis and excessive proliferation of cancer cells [34]. Deregulation of miRNA levels in a tumour may also be the result of structural genetic alterations, including: – chromosomal abnormalities, first found in a study by Calin et al. [28];  – mutations, as the inherited mutations in the primary miR-15 and miR-16 transcripts responsible for decreased miRNA expression in CLL [35];  – single nucleotide polymorphism, which has been described in lung cancer [36].

Overexpression of oncogenic miRNAs can reduce the amount of tumour suppressor gene products, although loss of tumour suppressor miRNA expression may result in an increase in the amount of oncogenic proteins [24]. Modulation of miRNA expression is a promising strategy in the treatment of cancer. Cimmino et al. [30] demonstrated that miR-15a and miR-16–1 can be used in the treatment of BCL2 overexpressing tumours, such as leukaemias or lymphomas, taking advantage of the fact that miRNAs reduce oncoprotein levels and consequently induce apoptosis. These miRNAs may also target several oncogene, such as MCL1, CCND1, and WNT3A [37]. Additionally, deregulation of miR-15 and miR-16 has been correlated with a better prognosis in CLL [38], and therefore they have potential for both therapy and disease monitoring.

MiRNA in EVB and HPV-associated cancers. It is estimated that about 12% of cancers are related to viral infections, with the vast majority in developing countries. It should be noted that the cancerogenesis requires other active factors, such as environmental mutagens, inflammation or immunosuppression; additionally, neoplasm growth caused by viruses usually occurs many years to decades after acute infection. In tumours, viral replication is reduced or absent, and viral genetic material may exist intracellularly as naked nucleic acid in the form of a plasmid, epismope, or genome integrated into the host cell [39].

Association of viruses and miRNAs in human tumours may be considered in several ways:

– expressed viral miRNAs promote tumour formation by inhibiting apoptosis, escaping infected cells from host immune surveillance, or modulating signaling [40, 41];

– genome damage due to the integration of foreign DNA affects not only the expression of the genes of tumour suppressor proteins (TS) but also the expression of microRNAs [42, 43];

– use of a viral infection associated with cancer and deregulation of human miRNAs [44, 45].

The Epstein Barr virus (EBV) is historically the first virus in which an miRNA was discovered [46]. This double-stranded herpes virus infects about 90% of people worldwide, and is found in all major types of lymphoma [47, 48]. EBV is detected in approximately 15% of diffuse large-B-cell lymphoma (DLBCL) cases [49]. MiRNA profiling by Imig et al. [49] showed that miR-424, -223, -199a-3p, -199a-5p, -27b, -378, -26b, -23a, -23b were increased, and miR-155, -20b, -221, -151–3p, -222, -29b/c, -106a were reduced by more
than 2-fold due to EBV infection of DLBCL. Increased levels of miR-21 have been associated with CLL, DLBCL and acute myeloid leukaemia [50]. Additionally, deregulated miR-21 expression is specific to many other cancers, including glioblastoma, lung cancer, squamous cell carcinoma, and breast cancer [51]. Rosato et al. [51] performed miRNA profiling of virus-infected and EBNA2 (Epstein–Barr virus nuclear antigen 2)-transfected U2932 DLBCL cell lines. MiR-21 has been shown to be positively regulated by this viral protein, confirming that EBNA2 can contribute to induced B cell transformation by altering miRNA expression.

Another example of lymphoma associated with EBV infection is Hodgkin’s lymphoma [49]. Jones et al. used quantitative real-time PCR (qRT-PCR) to study plasma miRNA levels of classical Hodgkin’s lymphoma patients, compared to healthy participants. Elevated levels of miR-21 along with miR-494 and miR-1973 have been reported in cancer patients. It should be noted that these miRNAs returned to normal after disease remission, but only miR-494 and miR-1973 reflected a temporary response to therapy. This allowed the disease response to the therapy to be indicated [52].

EBV is also associated with NK (natural killer) cell leukemia because it regulates the development of the NK cells from which this kind of cancer is derived. Infections caused by EBV result in immortalization of the lymphoid cells and may also contribute to the elevation of miRNA levels in biological fluids [43].

An oncogenic virus which, unlike EBV, does not encode viral miRNAs, is the small human papillomavirus (HPV) which exists as a spherical epimere in cells and contains a double strand DNA. It can be linearized and occasionally integrated into the host genome, which is the case with the common cervical cancer [32, 53]. The oncogenic effect of this virus is manifested by a change in gene expression [54]. A significant number of miRNAs have been shown to be located close to HPV integration sites, and miRNA genes are possible targets for genome changes induced by HPV integration into the host genome [31]. Many studies have revealed that some families of this type of RNA may be involved in the pathogenesis of HPV-related cancer (e.g. miR-15a, miR-16, miR-195, miR-497, miR-143 or miR-145). HPV deregulates these miRNAs through interactions in the viral oncoprotein pathways, which can lead, e.g. to inhibition of cell cycle arrest, and consequently contribute to carcinogenesis [55].

The HPV genome comprises six non-structural genes and two structural genes, Oncogenes can be distinguished among the first of these and include E6 and E7 [56]. Moreover, recent publications also show the involvement of the E5 gene as an oncogene [57, 58], which are committed in the HPV-related transformation, and target miRNAs associated with tumour progression or suppression. For example, the E6 and E7 genes increase the amount of oncopgenic miRNA-21, which negatively affects the expression of the tumour suppressor gene PTEN (phosphatase and tensin homolog) [56, 59]. Additionally, the expression of the E5, E6 and E7 genes in cervical cancer cell lines (SiHa, CaSk) has led to a reduction in the expression of some miRNAs that inhibit tumorigenesis, such as miRNA-22, miRNA-450 or miRNA-203 [60–62].

It is estimated that about one-fifth of oropharyngeal tumours are caused by HPV [45]. Variable amounts of miRNAs were observed in HPV-positive HNCSCC (head and neck squamous cell carcinoma) and the same tumour cell lines. Diversified expression of miRNAs has been reported in HPV-positive and HPV-negative samples. This suggests that altered miRNA expression may contribute to oncogenesis [44, 63, 64]. MiR-9 has been shown to be constantly detected in HPV positive HNSCC subgroups, and rarely in HPV negative HNSCC subgroups. This indicates the specificity of miR-9 for HPV-associated HNSCC. Due to the presence of HPV, HNSCC is divided into two groups: HPV positive with a better prognosis and HPV negative tumours with a worse prognosis [65]. Bersani et al. [66] demonstrated miR-155 overexpression in tonsillar and base of tongue cancer and linked it to HPV infection and improved survival. In contrast, low miR-185 expression was associated with negative HPV and decreased survival. Examples of miRNAs that may be used as biomarkers in the prognosis or diagnosis of cancers related to EBV and HPV infections are presented in Table 1.

### Table 1. MicroRNAs in neoplasms associated with HPV and EBV infection

| Oncogenic virus | Type of cancer | Upregulated miRNAs | Downregulated miRNAs | References |
|-----------------|----------------|---------------------|-----------------------|------------|
| HPV             | Head and neck cancer | miR-9; miR-16; miR-18a; miR-21; miR-31; miR-33; miR-363; miR-497 | miR-29a; miR-31; miR-139-3p; miR-142-5p; miR-143; miR-145; miR-181a; miR-181b; miR-195; miR-221; miR-222 | [55, 67–70] |
| Cervical cancer | miR-10a; miR-15b; miR-16; miR-21; miR-31; miR-127; miR-132; miR-133b; miR-145; miR-155; miR-214 | miR-23b; miR-26a; miR-29a; miR-34a; miR-99a/b; miR-133a; miR-145 | [71–81] |
| EBV             | Burkitt’s lymphoma | miR-127 | miR-28 | [82, 83] |
|                 | Head and neck cancer | miR-31; miR-155; miR-221/222 | miR-134; miR-204 | [84–88] |

Both HPV and EBV infections are associated with oral squamous cell carcinoma (OSCC), which accounts for approximately 95% of oral cancer cases, causing approximately 177,000 deaths annually, and late diagnosis is a significant problem in this case [89]. Despite the fact that the oral cavity can be readily examined, most tumours are diagnosed in the late stage, which reduces the survival rate of patients [90]. The markers of solid tumours used so far, such as carcinoembryonic antigen or carcinoantigen 19–9, have not shown sufficiently high sensitivity and specificity in the effective diagnosis of all oral cancers [91, 92]. It is known that some miRNAs are specifically associated with the presence of neoplasms, even in the early stages, which is important for the diagnosis of this neoplasm [93]. Increasing expression of miR-21 is associated with low survival in head and neck cancer patients [94]. This type of miRNA is also of interest due to the location of the miR-21 gene close to the HPV integration site [95], and creates an interesting link between cancers caused by these viruses and miR-21. Additionally, miR-223, miR-26a and miR-126 have been shown to be upregulated in oral cancer patients. Interestingly, a higher level of biomarker was found in healthy tissue adjacent to the tumour tissue compared to tumour tissue from patients with oral cancer [43, 89, 96, 97].

In a study by Yan et al., seven OSCC-related miRNAs were identified, three of which (miR-21, miR-31, miR-338) showed upregulation, while the others (miR-125b, miR-133a, miR-133b, miR-139) were downregulated [98]. Moreover,
Petronacci et al. [99] found altered expression of miR-497–5p and miR-4417 in OSCC samples and associated deregulated levels of these miRNAs with the proteoglycan pathway in cancer. These studies indicate the possibility of using miRNAs as biomarkers in the prognosis and diagnosis of head and neck cancers, such as OSCC. It should be noted that from the perspective of clinical use, further studies are required to confirm the sufficient sensitivity and specificity of miRNAs.

To date, several clinical trials of miRNA in cancer have been registered in the clinicaltrials.gov database. For example, the study entitled: MicroRNA Markers in Head and Neck Cancers (NCT04305366) investigates whether miRNA markers present in the body fluids of patients could provide prognostic or diagnostic clinical relevance in the treatment of cancer. Another example is a study that aimed to identify haematological malignancies, and predict treatment using microRNA as a diagnostic tool (NCT02791217). It should be noted that a large part of the research on these biomarkers is at the stage of collecting participants. The results, however, may provide important information on the use of specific miRNAs as biological markers in the future.

**EBV-encoded miRNAs.** Currently, many oncoviruses encoding miRNAs have been discovered, for example, the role of viral miRNAs in the pathogenesis of cancers associated with Kaposi's sarcoma virus has been shown [100]. EBV is also a virus encoding miRNAs. EBV encodes 44 BamHI-A rightward fragment-derived miRNAs (BART) and 4 BamHI-H rightward fragment 1-derived miRNAs (BHRF1) [101]. Expression of BHRF1 miRNAs depends on the type of viral latency, while BART miRNAs are expressed with all forms of latency [102]. EBV-encoded miRNAs are involved in inhibiting apoptosis, promoting B-cell survival, and avoiding recognition by the immune system [103]. Furthermore, it regulates viral mRNA transcripts [44].

Vereide et al. [104], using luciferase reporter assay, investigated whether caspase-3 is the target of BART miRNAs. Removal of the BART miRNA increased the level of caspase 3 protein, and reintroducing this miRNA decreased its amount. The results proved that EBV’s miRNAs support Burkitt’s lymphoma cells in the absence of other oncogenes by inhibiting apoptosis, and viral miRNAs promoted the transformation of primary B cells [104, 105].

Several functions of viral RNA in nasopharyngeal cancer have been confirmed in research [41–43, 45]. In this neoplasm, EBV-encoded miR-BART is highly expressed and may provide important information on the use of specific miRNAs as biological markers in the future.

**CONCLUSIONS**

The prospect of using non-invasive molecules found in biological fluids is very promising. MiRNAs such as miR-21 may be used in the future on a large scale in the diagnosis and treatment of cancer diseases associated with viral infections. Currently, several miRNA-based drugs are at different stages of clinical studies, and modern molecular advances in biology, such as next-generation sequencing, can significantly contribute to faster discovery in these non-coding RNAs. The findings in the field of miRNA expression levels with viral associated neoplasms could provide much relevant information regarding the regulation of oncogenesis; however, knowledge and research about these short nucleotide sequences has to be constantly expanded.

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Marcin Kolesnìk, Ewa Stepien, Malgorzata Polacz-Dacewicz. The role of microRNA (miRNA) as a biomarker in HPV and EBV-related cancers

Journal of Pre-Clinical and Clinical Research 2021, Vol 15, No 2

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