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REVIEW ARTICLE

Human Papillomavirus Infections, Cervical Cancer and MicroRNAs: An Overview and Implications for Public Health

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Abstract: Human Papillomavirus (HPV) is among the most common sexually transmitted infections in both females and males across the world that generally do not cause symptoms and are characterized by high rates of clearance. Persistent infections due at least to twelve well-recognized High-Risk (HR) or oncogenic genotypes, although less frequent, can occur, leading to diseases and malignancies, principally cervical cancer. Three vaccination strategies are currently available for preventing certain HR HPVs-associated diseases, infections due to HPV6 and HPV11 low-risk types, as well as for providing cross-protection against non-vaccine genotypes. Nevertheless, the limited vaccine coverage hampers reducing the burden of HPV-related diseases globally. For HR HPV types, especially HPV16 and HPV18, the E6 and E7 oncoproteins are needed for cancer development. As for other tumors, even in cervical cancer, non-coding microRNAs (miRNAs) are involved in post-transcriptional regulation, resulting in aberrant expression profiles. In this study, we provide a summary of the epidemiological background for HPV occurrence and available immunization programs. In addition, we present an overview of the most relevant evidence of miRNAs deregulation in cervical cancer, underlining that targeting these biomolecules could lead to wide translational perspectives, allowing better diagnosis, prognosis and therapeutics, and with valuable applications in the field of prevention. The literature on this topic is rapidly growing, but advanced investigations are required to achieve more consistent findings on the up-regulated and down-regulated miRNAs in cervical carcinogenesis. Because the expression of miRNAs is heterogeneously reported, it may be valuable to assess factors and risks related to individual susceptibility.

Keywords: E6 oncoprotein, E7 oncoprotein, immunization programs, miRNA, oncoviruses, tumor biomarkers.

1. INTRODUCTION

Infectious agents are responsible for 20-25% of all cancer cases worldwide [1]. It has been estimated that nearly 15% of human cancers are associated with viral infections [2, 3], and in this context, a number of different viruses can contribute to several steps into carcinogenic processes. Among these viruses, Human Papillomavirus (HPV) has a prominent position, causing 30% of all infectious agent related cancers [4].

HPVs are extremely diverse at the level of genotype, epithelial tropism, and pathogenicity, being classified into cutaneous and mucosal groups [5]. HPVs are further divided into Low-Risk (LR) and High-Risk (HR) types, depending on the lesion propensity for malignant progression [6, 7]. Among more than 200 recognized HPV genotypes, HPV5 and HPV8 are the most commonly associated with cutaneous squamous cell carcinoma in patients with epidermodysplasia verruciformis [8]. The LR mucosal HPVs, especially HPV6 and HPV11, commonly cause genital warts, while the mucosal HR HPV16 and HPV18 are primarily involved in squamous intraepithelial lesions, which can progress to invasive squamous cell carcinoma [8, 9], even though different oncogenic types are becoming emergent [10, 11]. While HPVs have been associated with oral and numerous malignancies, including cancers of head and neck, anus, vulva, vagina, and penis, the infections are responsible for nearly all cervical cancers [7].

HPV outcomes could be avoided through the adoption of prophylactic measures, mainly with vaccination. The currently available immunization strategies have been shown to be effective in reducing genital warts, cervical disease, and

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anogenital dysplasia, but global vaccination rates are still under the required target level [12], including in Italy [13].

Understanding of the natural history of HPV infection and cancer progression requires a holistic epidemiological and clinical approach, taking into account the essential features related to cellular and molecular biology, transcriptional and post-transcriptional regulation. During malignancy progress, HPV genome integration into the host cell results in the primary viral E6 and E7 oncoproteins, whose overexpression contributes to cervical carcinoma development [6], inhibiting the functions of tumor suppressor p53, and promoting degradation of Retinoblastoma protein (pRb), respectively [8, 9].

In cervical cancer, as well as in many other tumors, short, non-coding single strands of RNAs, named as microRNAs (miRNAs), play a critical role, since their deregulation has been widely observed [14, 15]. Oncogenic viruses express miRNAs that may regulate their own gene expression, as well as influence the host's gene expression [16]. Contribution of miRNAs into the carcinogenic processes can be summarized as follows: miRNA genes can be located at susceptible sites in the genome/regions amplified or deleted in human cancers; since miRNAs are involved in the control of cell proliferation and apoptosis, their deregulation may contribute to proliferative diseases, including cancers; altered miRNA expression has been observed in malignant tumors and tumor cell lines compared to normal tissues [17, 18].

In this study, due to the continuous evolution of the epidemiological patterns related to these viruses, which are responsible of the most common sexually transmitted infections, and the high burden of the induced cancers, we reviewed the latest available evidences on HPV occurrence and immunization programs, tailored for the principal risk groups, and provided a description of the significant aspects concerning the miRNAs expression in cervical cancer in the current vaccination era.

2. HPV INFECTIONS AND CANCERS: EPIDEMIOLOGICAL PICTURE AND TARGETED IMMUNIZATION STRATEGIES

HPVs, double-stranded DNA tumor viruses belonging to the *Papillomaviridae* family, represent the most frequent viral agents involved in infectious agents-associated oncogenesis [16], with peak prevalence in early adulthood [19]. Approximately, 280 papillomavirus types are described in vertebrates, and over 200 types can infect humans [20]. While infections usually do not cause symptoms, resolve spontaneously [21] and are generally cleared by the immune system within 1-2 years of onset, 10-20% can latently persist, leading to progression towards precancerous lesions, as well as to various forms of invasive cancer [22]. Furthermore, the persistence of HR HPV infections represents the main risk factor for cancer development [19].

Indeed, it is well known that all HPVs, mainly LR HPV6 and HPV11 genotypes, can induce proliferative benign lesions at the site of infection, such as papillomas or warts [23]. However, at least 12 viral types, HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59, are highly related with malignant neoplasms [7, 19], and are classified as HR HPVs into Group 1 carcinogenic agents by the International Agency for Research on Cancer [5, 24]. Additional 13 HPVs were classified as either probably, or possibly, carcinogenic (Group 2A and B) based on the limited evidence and/or their close phylogenetic placement with other carcinogenic HPVs [5].

HR HPVs are not only responsible for almost all cases of cervical cancer, but also for a substantial proportion of vulvar, vaginal, penile, anal, oropharyngeal, and cutaneous squamous carcinomas [25]. Current epidemiological data confirm that HPV16 represents the most recurrent HR HPV identified in cervical cancers, but also is the most common in all HPV-related cancer sites, followed by HPV18 [7, 26, 27], which together approximately account for more than 70% of all cases of squamous cell carcinoma [28].

To date, HPV remains the most common sexually transmitted infection, and despite the availability of prevention strategies, the associated cancers represent one of the foremost causes of morbidity and mortality globally [29]. Epidemiological data regarding the global disease burden underlines that HPV is responsible of 630,000 (4.5%) new cancer cases worldwide per year: 570,000 (8.6%) cases per year in women, and 60,000 (0.8%) cases in men [30, 31]. Cervical cancer represents the second most common neoplastic pathology among women [7, 32], and accounts for 83% of HPV-attributable cancer [30], with an estimated 500,000 diagnosed cases each year, resulting in more than 250,000 deaths [33].

Since the past three decades, increased rates of anal cancer have been also reported, globally accounting for 35,000 cases per year (half occurring in men), with a high proportion associated with the HR HPV16 and HPV18 types. Furthermore, 13,000 penile and 12,000 vaginal cancer cases, 8,500 cases of vulvar carcinoma, and 38,000 head and neck cancer cases have been attributed to HPV, of which 21,000 cases are oropharyngeal cancers, occurring in most developed countries [30]. HPV-attributable head and neck squamous cell cancers are mainly represented by Oropharyngeal Cancers (OPCs), which have two distinct etiologies: the HPV infection, with a proportion of cases alarmingly increasing in some high-income countries, and the additional risk factors from tobacco/alcohol consumption [34]. HPV-positive OPC patients are epidemiologically and clinically distinct compared with their HPV-negative counterparts, being younger, and having less exposure to tobacco and alcohol, higher socioeconomic and educational status with better outcomes [35]. In the newly published 8th edition TNM (using the "tumor - T" (extent of primary tumor), "lymph node - N" (absence/presence and extent of overt regional lymph nodes), and "metastasis – M" (absence/presence of distant metastasis) attributes) [36, 37] stage system for head and neck cancer, significant changes have been introduced to HPV-mediated OPC [38-40]. HPV-specific staging is necessary for several reasons: relevance to discussion with patient/family; clinical trials design since HPV-positive and HPV-negative OPCs are separately addressed; and practice guidelines may be different; separate classification for HPV-

positive and negative OPCs may be further applicable for both clinical care and cancer surveillance [38].

Prophylactic HPV vaccines based on recombinantly expressed virus-like particles, with direct and indirect effects by cross-protection against HPV types not included in the formulations, have been developed, following two main approaches: one targeting young women prior to sexual debut, and the other including young men of the same age range [12].

To date, three vaccines licensed for use by the US Food and Drug Administration (FDA) have demonstrated a robust immune response [41], and have been recommended at age 11 or 12 years [42]. The Advisory Committee on Immunization Practices also recommends vaccination for females aged 13 through 26 years and males aged 13 through 21 years not previously vaccinated, and through age 26 years for men who have sex with men and immunocompromised subjects (including those with HIV infection) whether not previously vaccinated [42]. However, a universal vaccination strategy would have a huge impact, because it could be effective for preventing up to 90% of HPV-related diseases. In particular, current vaccination is available through: bivalent HPV (2vHPV) vaccine approved since 2009 (Cervarix; Glaxo SmithKline, Rixensart, Belgium) targeting HR HPV16 and HPV18; quadrivalent HPV (4vHPV) vaccine approved since 2006 (Gardasil; Merck & Co, Inc., Whitehouse Station, NJ) protecting against LR HPV6 and 11, and HR HPV16, and HPV18; nonavalent HPV (9vHPV) vaccine introduced in 2014 (Gardasil 9, Merck & Co, Inc. Whitehouse Station, NJ) for preventing infections by LR HPV6 and 11 and HR HPV16 and 18, and five additional oncogenic types, HPV31, 33, 45, 52, 58 [43]. The nonavalent vaccine was approved by FDA for use in females and males aged 9-14 years and represents, as from 2016, the only vaccine available for use in the United States, due to broader coverage against HR HPVs, while Cervarix® and Gardasil® for males and females aged 11-12 years are still used in other countries, including Italy.

Starting with vaccines against 2vHPV and 4vHPV, which became available more than 10 years ago, over 80 countries introduced a national HPV vaccination program, and as of 2016, globally it has been estimated that 1.4% of the total population and 6.1% of women aged 10-20 years received a full vaccine course, with a heterogeneous coverage among countries [12]. It has been reported that 33.6% of females aged 10-20 years received the full course of the vaccine in highly developed countries compared to 2.7% in less developed ones [44].

In Europe, analysis of full-course vaccination by geographical region revealed that coverage among the female population was 4.3% (14 million) and that 68% of the vaccinated women were predominantly from high-income countries, as compared to 28% from upper-middle-income countries. In particular, Australia and New Zealand reported the highest age-specific coverage rates, reaching nearly 70% of females aged 15-19 years. Therefore, the vaccination compliance rate is still far from the ideal threshold, underlining the urgent need to address effective strategies and to overcome vaccination barriers.

In Italy, the latest data related to HPV vaccine coverage up to December 2017 among females aged 12-20 years revealed a lower coverage in the primary vaccination group aged 12 years as compared to other age groups [45]. In the oldest cohorts (1997-2001) to whom vaccination was offered at no cost in most of the Italian regions until the eighteenth year, coverage for at least one vaccine dose was 73-76%, and 69-72% for the complete cycle. Therefore, the national HPV vaccination coverage in girls is still below the 95% optimal threshold as established by the National Vaccine Prevention Plan 2017-2019. At the regional level, 95% coverage for all cohorts is not reached in any Region, whilst the coverage in boys is very far from the objectives by the National Vaccine Prevention Plan, which has indicated a gradual 60% threshold for 2017 up to 95% in 2019 [45]. The wide variability of vaccination coverage amongst Italian regions underlines that targeted interventions are needed in specific geographical contexts, and that, although the anti-HPV vaccination is not comprised within the mandatory vaccinations by the Italian law n. 119/2017, it is included within the so-called "Essential Level of Care" (Livelli Essenziali di Assistenza-LEA), which must be guaranteed to all citizens by every Region.

3. INSIGHTS ON MiRNA AND CERVICAL CANCER

MiRNAs are short 18-25 nucleotide non-coding RNAs that bind to the target mRNA typically in the 3'-untranslated region (3'-UTR) [46], causing mRNA degradation, or ceasing their translation. There are two principal mechanisms associated with miRNA functions: first, miRNAs bind specifically to sites in the 3'-UTR of targeted mRNAs, resulting in mRNA degradation; second, miRNAs exert partial base complementarity to the targeted mRNAs and suppress the translation processes, inhibiting protein synthesis. However, each miRNA may target more than 100 mRNAs, and at the same time, each mRNA may contain multiple binding sites for different miRNAs [47].

Research showed that these small molecules are involved in the expression of at least one-third of human genes [48], and that their functions can provide various translational applications in cancer, mainly for diagnostic, prognostic, and therapeutic approaches [49, 50]. By interfering with mRNA translation, miRNAs act as post-transcriptional regulators of gene expression, playing extensive effects on cellular functions, such as development, differentiation, proliferation, inflammation, immune responses, stress responses, apoptosis, invasion, and metastatization [51], thus with high potential to be used as diseases biomarkers [49].

Aberrant (dysregulated) miRNAs expression, with silencing or over-expression (de-silencing), has been demonstrated in several tumor types, including cervical cancer cell lines, acting as either oncogenic or tumor-suppressive agents [52, 53]. Despite evidence reporting critical roles of miRNAs in the carcinogenesis, it remains unresolved whether altered miRNAs expression is the cause or the consequence of malignant transformation [54, 55].

Oncoviruses, like HPV, express miRNAs that can significantly contribute to carcinogenic processes by regulating viral gene expression or influencing host gene expression [16]. The major mechanisms involved in carcinogenesis encompass the de-regulation of oncogenes and tumor suppressor genes by viral genome integration into host genome (*i.e*., HPV, retroviruses), and the modulation of viral oncogenes expression (*i.e*., herpesviruses) by causing DNA damage and host cell transformation through the inactivation of major regulators of genome stability and cell cycle [16].

The HPV genome is characterized by early-region genes E1-E7 encoding for the regulatory proteins E1, E2, E4, E5, E6, and E7, followed by a late region with L1 and L2 capsid proteins, a long control region with regulatory sequences, and a viral origin of replication [56]. Amongst all, E6 and E7 represent the main oncoproteins in HPVs, whose overexpression is a pre-requisite for tumor development being necessary and sufficient for HPV-mediated oncogenesis [5]; the E5 protein also contributes to increased cancer risk [57]. In particular, the E6 protein inactivates tumor suppressor p53 function [9, 58], whereas protein E7 binds Rb retinoblastoma protein, which is involved with cell cycle progression [9]. The virus integration into the host genome is a crucial event in HPV-related carcinogenesis and influences the stage of the disease and tumor type (cervical, anal, penile, head and neck cancer, *etc*.) [59].

During a persistent infection correlated with cervical lesions, HR HPV E6 and E7 can promote DNA damage *via* p53 and pRb inactivation, resulting in the impaired DNA checkpoint controls, leading to the subsequent transformation into cancer cells [9]. Hence, profiling expression of miRNAs in HPV-related malignancies is pivotal for identifying novel biomarkers for pre-malignant stages and for patients who require individualized treatments [60-62].

In the last decade, numerous studies have been conducted to better understand the role of miRNAs in HPV-related tumors, particularly cervical cancer [47, 63-66], although findings are generally contradictory. In detail, there are oncomiRs that include miRNAs significantly over-expressed in tumor tissues during HPV infection and lead to the onset of aberrant cell proliferation and growth [67], and tumor suppressor miRNAs that are under-expressed in HPV-positive tumors compared with normal non-cancerous tissues [68].

Generally, a differential miRNAs expression in invasive HPV positive squamous cell carcinomas compared to control tissue has been observed [69-73], revealing up- or down-regulation (Table **1**) of specific miRNAs [54]. Indeed, the abnormal/altered expression of miRNAs leads to tumor genesis and modulate disease progression (Fig. **1**), as well as variations in different cervical cancer stages (*i.e*., Cervical Intraepithelial Neoplasia - CIN grade I, II, and III) [73]. Furthermore, an increasing number of dysregulated miRNAs during the progression of CIN1-3 to cervical cancer has been reported. Several mechanisms can control miRNA expression, and are associated with the combination of chromosomal defects, such as deletions, amplifications or mutations with other genetic/epigenetic events, causing up- or down-regulation of miRNAs [74].

Table 1. miRNAs with up-regulated and down-regulated expression levels in cervical cancer.

MiRNA	References
Up-regulation	
miR-9	[60, 63, 65, 75-82]
miR-10a	[60, 64, 65, 75, 83]
miR-16	[52, 61-64, 75, 84]
miR-17	[75, 84-87]
miR-20a	[60, 66, 86, 88-93]
miR-20b	[65, 72, 75, 79, 84, 89, 94, 95]
miR-21	[52, 61, 70, 71, 75, 76, 78, 84-87, 90, 96-114]
miR-27a	[53, 62, 64, 85, 115, 116]
miR-31	[62, 71, 76, 85, 89, 96, 98, 117-120]
miR-92a	[62, 66, 75, 118, 121-125]
miR-93	[75, 84, 89, 118, 126, 127]
miR-106a	[64, 75, 84, 118, 128, 129]
miR-146a	[52, 75, 90, 103, 130, 131]
miR-155	[52, 53, 75, 78, 79, 84, 117, 118, 132-134]
miR-196a	[60, 64, 135-139]
miR-199b	[63, 79, 85, 140, 141]
miR-200a	[61, 75, 89, 105, 117, 126, 142]
miR-205	[52, 64, 85, 117, 138, 143-145]
miR-210	[66, 82, 85, 89, 146]
Down-regulation	
miR-29a	[52, 62, 64, 84, 90, 118, 147, 148]
miR-34a	[53, 73, 79, 86, 90, 114, 132, 149-154]
miR-99a	[61, 64, 73, 75, 89, 110, 118]
miR-100	[52, 62, 89, 75, 84, 86, 118, 155, 156]
miR-125b	[52, 61, 78, 75, 84, 117, 118, 151, 157]
miR-126	[52, 86, 117, 158-160]
miR-143	[52, 64, 69, 70, 85, 89, 99, 117, 148, 161-164]
miR-145	[52, 64, 69, 77, 84, 85, 89, 118, 139, 165-169]
miR-149	[61, 63, 75, 84, 85, 170]
miR-193b	[61, 65, 75, 79, 96]
miR-195	[52, 75, 76, 78, 84, 89, 110, 118, 171-175]
miR-203	[53, 61, 63-65, 75, 79, 85, 86, 90, 176]
miR-214	[89, 98, 126, 177-183]
miR-218	[69, 71, 73, 75, 76, 89, 110, 118, 147, 150, 184-191]
miR-375	[75, 84, 118, 150, 192, 193]
miR-424	[52, 78, 117, 118, 150, 194-198]
miR-497	[69, 75, 76, 84, 89, 199, 200]

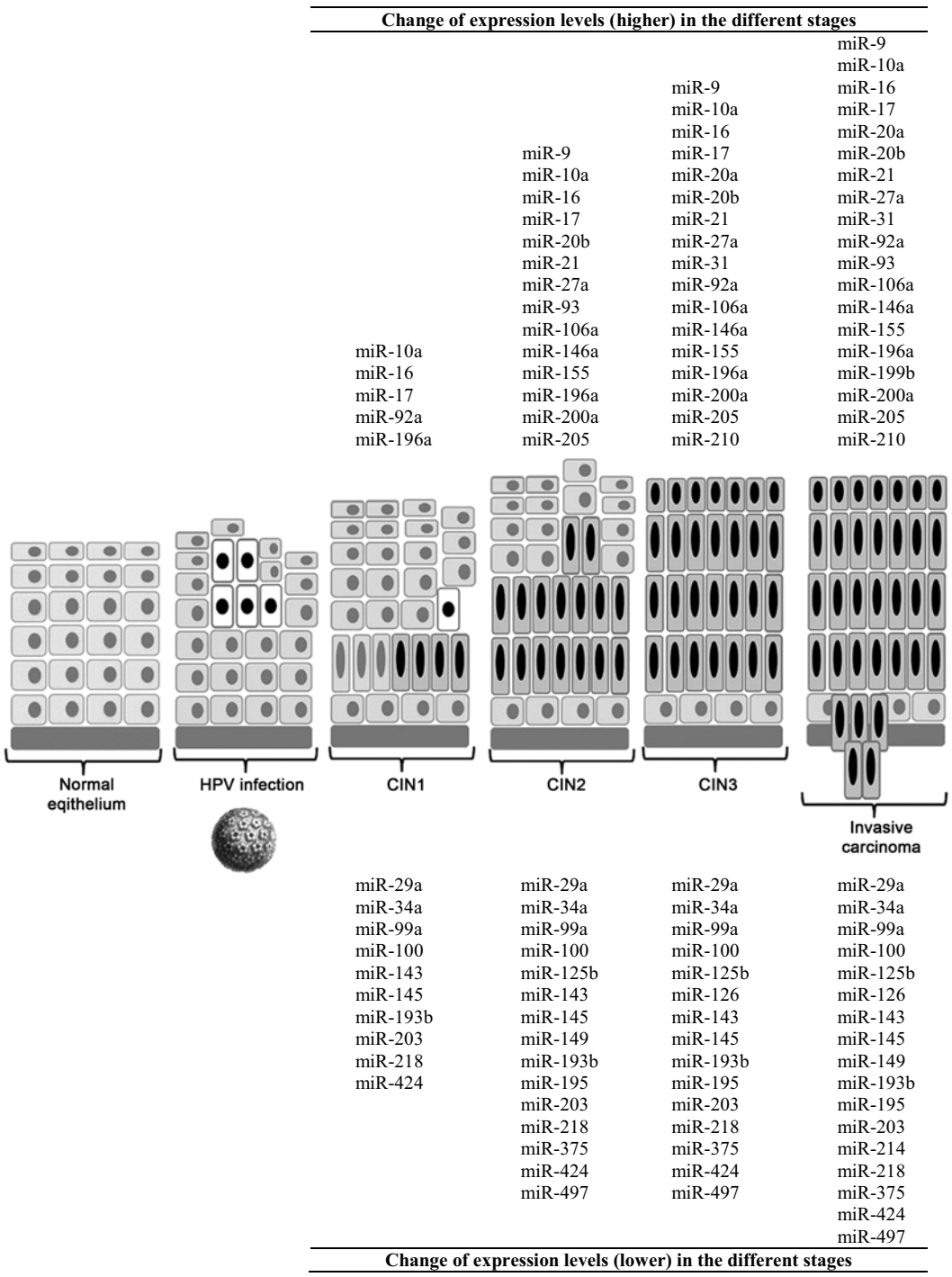

Fig. (1). Interaction between cervical epithelium, HPV infection, and the most significant miRNAs dysregulated in the cervical cancer progression (modified from Pardini *et al*. [14]).

As shown in Table **1**, many studies investigated the role of miRNAs involved in the development of cervical cancer, underlining their crucial biological roles. Findings achieved from the available studies indicate that over 250 miRNAs are expressed differently in cervical cancer, being up- or down-regulated.

In the present report, we described the most relevant miRNAs and their function at different stages in the cervical cancer progression (cited in at least 5 articles with similar findings; Table **1**). Among the up-regulated miRNAs, miR-21 and miR-155 have been widely reported to promote cell migration and invasion (Fig. **1**), as well as lymph node metastasis in cervical cancer [52, 53, 66, 70, 71, 75, 76, 78, 79, 84-87, 90, 96-114, 117, 118, 132-134]. Additional up-regulated miRNAs have been involved in the initiation and progression of cervical carcinogenesis, since the aberrant expression of miR-20b, miR-31, miR-92a, miR-146a, and miR-205 positively correlated with cell proliferation, enhance-

ment of the migration and invasion abilities of cancer cells, and vessel invasion [52, 62, 64-66, 71, 72, 75, 76, 79, 84, 85, 89, 90, 94-96, 98, 103, 117-125, 130, 131, 138, 143-145]. Furthermore, the up-regulation of miR-196a has been linked to an enhanced proliferative ability of cervical cancer cells, advanced tumor stage, and poor overall survival in patients [60, 64, 135-139], and miR-9 expression has been found significantly over-expressed in squamous cervical cancer [60, 63, 65, 75-82].

Different miRNAs are down-regulated as well, such as: miR-34a and miR-214, both promoting cell proliferation, migration, invasion, and angiogenesis [53, 73, 79, 86, 89, 90, 98, 114, 126, 132, 149, 150-154, 177-183]; miR-143, involved in the regulation of cell migration and invasion [52, 64, 69, 70, 85, 89, 99, 117, 148, 161-164]; miR-145, whose low expression levels were significantly associated with poor cancer differentiation and lymph node metastasis [52, 64, 69, 77, 84, 85, 89, 118, 139, 165-169]; miR-195, whose reduced expression has been associated to advanced clinical stage in cancer patients and lymph node metastasis [52, 75, 76, 78, 84, 89, 110, 118, 171-175]; miR-203, linked to lymph node metastasis [53, 62-65, 75, 79, 85, 86, 90, 176]; miR-218, associated with cell migration and invasion, induction of epithelial-mesenchymal transition and invasion [69, 71, 73, 75, 76, 89, 110, 118, 147, 150, 184-191]; miR-375, involved in cell proliferation, migration and invasion, modulation of epithelial-mesenchymal transition and correlated with pelvic lymph node metastases [75, 84, 118, 150, 192, 193]; miR-424, positively correlating with poor tumor differentiation, advanced clinical stage, lymph node metastasis and other low prognostic clinical/pathological parameters [52, 78, 117, 118, 150, 194-198]. Interestingly, the expression levels of miR-34a, miR-218, miR-375, and miR-424 have been found decreased simultaneously to an increase of disease severity [14].

CONCLUSION

miRNAs regulate diverse biological processes in the host-pathogen interactions and represent an attractive target due to the critical function in several signaling pathways. These small biomolecules are commonly encoded by viruses that undergo long-term persistent infection, including HPV, and can act as oncogenes to promote carcinogenesis, or as tumor suppressors targeting oncogene mRNAs. The miRNAs dysregulation causes abnormal cell growth and differentiation, leading to cancer and many other diseases. Indeed, miRNA expression profiles have been found to be highly altered in several cancers compared to healthy controls.

Papillomaviruses can cause several types of cancers, but only persistent infections can lead to malignant tumors. Although oncogenic genotypes are etiologically associated with cervical cancer, the HPV infection alone is not sufficient to induce the malignant transformation and to explain the development of cervical cancer, implying that molecular factors at multiple levels should be considered, including miRNAs and their altered expression profiles. Hence, a systematic and rigorous appraisal of the alterations of miRNAs during oncogenic HPVs transformation can significantly improve knowledge of cervical carcinogenesis processes, with potentially enormous public health impact in drawing successful diagnostic, prognostic, and therapeutic strategies.

Tumors related to oncoviruses, including HPV, have been extensively studied with the aim to detect markers and treatment targets. Studies focused on cervical cancer molecular epidemiology predominate, as it is the most common malignancy in women worldwide. Public health efforts should be implemented to reduce the attributable morbidity and mortality that can be achieved only with significant improvements in all levels of prevention, particularly reinforcing and supporting vaccination compliance.

Cervical cancer cells display the aberrant expression of a considerable number of miRNAs, both oncogenic and tumor-suppressive, and specific up-regulated or down-regulated miRNAs have been shown to correlate with tumors. Despite the uncertainty in the functional effects of the miRNAs dysregulation on the cervical oncogenesis, the evaluation of their expression profiles have already provided noteworthy insights, and might also be valuable to assess factors and specific risks related to individual susceptibility, as well as useful for the clinical histopathological classification. Since miRNAs expression is altered in cancer tissues, investigation of the differential profiles of certain miRNAs may lead to crucial advancements for cancer diagnosis, facilitating disease classification and monitoring its development and progression, prognosis, and treatment.

The present study provides an overview of the contribution of miRNAs into cervical cancer, focusing on the recently available evidence, which is somewhat contradictory about their influence on gene expression in the human host. Several differentially expressed miRNAs in cervical cancer tissues or cells have been reviewed, but it could not be concluded on a validated panel of viral miRNAs in cervical infected cells. Despite the extensive studies carried out, to date, no widely accepted HPV-encoded miRNAs signature can be definitely recognized, maybe due to the lack of broadly applicable methodology and of suitable/standardized laboratory models, which are required. Although additional investigations are consistently needed for a better comprehension of miRNAs pathways and expression profiles that can significantly improve the understanding of epidemiology of HPV infections and related diseases, the reviewed evidence underlines the emerging role of miRNAs in cervical carcinogenesis mechanism as key mediators of gene expression, and the usefulness of tracking their deregulation as potential predictive biomarkers in the field of infectious diseases prevention and therapeutic decisions remains to be established. Promising applications of miRNAs could also be addressed for the improvement of vaccination programs since the current HPV-targeting vaccines are effective for preventing infections and neoplastic diseases, but the established or pre-existing infections could not be cleared, being the target antigens not expressed in the infected basal epithelial cells [201-203].

In conclusion, miRNAs could represent effective markers of progression of pre-neoplastic lesions to invasive and metastatic disease, providing a dynamic prognostic factor. Therefore, since miRNAs have a vital role in all stages of cervical cancer progression, from cell invasion and migration to eventual tumor metastasis, the combined use of a selected panel of oncomir and tumor suppressor miRNAs could provide an enhanced diagnostic and prognostic approach, with increased accuracy with respect to any single miRNA marker.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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