miR-23b-3p, miR-124-3p, and miR-218-5p Regulate Cervical Cancer Progression

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In cervical cancer (CC), miR-23b-3p, miR-124-3p, and miR-218-5p have been found to act as tumor suppressors by regulating cellular processes related to progression and metastasis.

Keywords: miRNAs ; cervical cancer ; bioinformatic analysis ; miR-23b-3p ; miR-124-3p ; miR-218-5p

1. Introduction

Cervical cancer (CC) is the fourth most common cancer diagnosed and the fourth cause of cancer death among women in the world. In 2020, 604,127 new cases of CC were diagnosed, and 341,831 deaths occurred due to this malignancy [1]. About 85% of deaths occur in developing or underdeveloped countries [2]. Most cases of CC are the result of persistent infection with genotypes of high-risk oncogenic human papillomavirus (HR-HPV), among which HPV-16 and HPV-18 are the most frequent [3][4][5]. The integration of viral DNA into the host cell genome and the overexpression of the E6 and E7 proteins of HR-HPV are key events for the initiation of cervical carcinogenesis. Viral oncoproteins, E6 and E7, directly or indirectly modulate the expression of multiple genes, which participate in the regulation of various stages of the viral cycle and cellular processes that contribute to cancer progression [2]. Through their interaction with various cellular proteins, E6 and E7 activate Fas, MAPK, Akt, PI3K, and Wnt signaling pathways, which modulate cellular proliferation, migration, invasion, and apoptosis, as well as epithelial–mesenchymal transition (EMT) and metastasis [6][7][8][9][10][11], cellular processes that modulate CC progression [12][13][14]. The dysregulation in the function of proteins, signaling pathways, and cellular processes, result from altered gene expression [15][16]. Viral oncoproteins, the accumulation of genetic and epigenetic alterations, and post-translational modifications lead to the inactivation of tumor suppressor genes, activation of oncogenes, and increase or decrease the expression of microRNAs (miRNAs) [17][18]. Alterations in miRNA expression are a causal factor in cancer progression and may be determinants of tumor aggressiveness [19].

MicroRNAs regulate the expression of several genes and thus modulate biological processes [20] such as cell proliferation, apoptosis, replicative immortality, immune response evasion, metabolic reprogramming, invasion, and metastasis [21][22][23][24][25]. On the other hand, messenger RNA (mRNA) contain different numbers of miRNA recognition elements (MREs), specific for individual miRNAs, in their 3′-UTR region. Thus, several miRNAs can hybridize with their specific MREs in one mRNA and a transcript can be simultaneously regulated by more than one miRNA [26]. In line with the above, miRNAs may play a synergistic or additive role in the cellular processes that they regulate [27][28][29].

In CC, the expression pattern of miRNAs is characterized by a decrease in tumor suppressor miRNAs and an increase in oncogenic miRNAs (oncomiRs) [30][31]. The methylation status in the miR-124-2, miR-218-1, and miR-218-2 promoters increased as the severity of the lesions increased and was significantly higher in CC. The increase in methylation was related to a decrease in the relative expression of these miRNAs. No significant changes were found in the methylation of miR-23b [32]; however, miR-23b-3p was found to be decreased in CC tissues and cell lines [33]. Inhibition of methylation in the miR-23b-3p promoter induced increased miRNA expression and decreased proliferation, migration, and invasion of CaSki HPV-16$^+$ cells. In C-33A HPV$^-$ cells, increased expression of miR-23b-3p was associated with decreased proliferation and invasion. The results indicate that miR-23b-3p is a tumor suppressor that modulates CC progression [34]. On the other hand, Li et al. found low expression of miR-124-3p in biopsies and CC cell lines, and demonstrated that this miRNA regulates proliferation, invasion, and apoptosis [35]. Likewise, Liu et al. demonstrated that, in biopsies, HeLa HPV-18$^+$ cells, C-33A, and SiHa HPV-16$^+$ cells, miR-218-5p is under-expressed and regulates proliferation, migration, and invasion [36]. Negative regulation of miR-23b-3p, miR-124-3p, and miR-218-5p expression in CC tissues and cell lines with and without HPV suggests that the virus does not fully determine miRNA-tumor suppressive function.

2. miR-23b-3p, miR-124-3p, and miR-218-5p Regulate Cervical Cancer Progression

miR-23b-3p, miR-124-3p, and miR-218-5p regulate different transcripts involved in processes related to the maintenance and progression of cancer [37]. The decrease of miR-23b-3p, miR-124-3p, and miR-218-5p in CC causes an increase in the level of their target mRNAs, including *MAPK1* and *c-Met*, *RGB2* and *AEG-1*, and *Gli3* and *ROBO1*, respectively, which promote cell proliferation, migration, and invasion, and inhibit apoptosis [35][38][39]. In CC cell lines C-33A, HeLa, SiHa, and CaSki, it was found that miR-23b-3p, miR-124-3p, and miR-218-5p are involved in the modulation of proliferation, EMT, migration, invasion, metastasis, and apoptosis, through the regulation of their target genes [20][32][34][40][41][42][43][44]. Li et al. found that, in HeLa cells, the overexpression of miR-23b-3p correlates with a decrease in cell proliferation and invasion and with an increase in apoptosis [38]. Likewise, the increase of miR-124-3p levels in HeLa and SiHa cells induces a decrease in cell proliferation and invasion, accompanied by an increase in apoptosis [35]. In a similar way, the upregulation of miR-218-5p decreases the proliferation, migration, and invasion processes of HeLa, SiHa, and C-33A cells [36]. These findings suggest that miR-23b-3p, miR-124-3p, and miR-218-5p are three tumor suppressor miRNAs that regulate the same cellular processes involved in CC progression.

One research workgroup found that miR-23b-3p is decreased in HPV-16$^+$ CC tissues and in C-33A, HeLa, and CaSki cells [32][33][34]. The ectopic overexpression of miR-23b-3p or the inhibition of methylation in the promoter region of miR-23b-3p significantly reduces *c-Met* expression in C-33A and CaSki cells. *c-Met* has five MREs for miR-23b-3p in its 3′-UTR region. c-Met is a tyrosine kinase receptor that activates Gab1 and FAK, and the signals stimulated by c-Met promote cell proliferation, migration, and invasion. A decrease in c-Met reduces proliferation, migration, and invasion in CaSki cells, as well as proliferation and invasion in C-33A cells [34]. On the other hand, in patients with CC, low levels of miR-23b-3p are associated with lower survival and predict a poor prognosis for women with this malignancy; restoration of miR-23b-3p expression reduces the activity of the AKT/mTOR signaling pathway and interferes with the progress of EMT, thereby decreasing the proliferation, migration, and invasion of SiHa and CaSki cells. *SIX1* is a direct target of miR-23b-3p and regulates, at least in part, the functional effects of this miRNA on CC progression [43]. Furthermore, the overexpression of miR-23b-3p induces a decrease in uPA protein levels, a urokinase that participates in the degradation of the extracellular matrix. In this way, this miRNA interferes with the migration of SiHa and CaSki cells [45].

The astrocyte elevated gene-1 (*AEG-1*), also known as metadherin (*MTDH*), is considered an oncogene whose overexpression contributes to carcinogenesis and tumor progression in various malignancies. In CC, *AEG-1* overexpression is associated with a poor prognosis. *AEG-1* is a direct target of miR-124-3p and has been found to be significantly increased in CC and in SiHa and HeLa cells; in contrast, miR-124-3p is decreased in CC tissue and in HeLa, SiHa, CaSki, and C-33A cells. In vitro, the restoration of miR-124-3p causes a decrease in *AEG-1*, along with decreased cellular proliferation, migration, and invasion, and a reduced progression of EMT in HeLa and SiHa cells. The increase in miR-124-3p correlates with an increase in E-cadherin and B-catenin and with low levels of N-cadherin, Twist, vimentin, and MMP9. Changes in the expression of these proteins indicate that miR-124-3p has a role in the regulation of EMT and metastasis. In line with this, the overexpression of miR-124-3p also results in a decrease in AKRIC2 and an increase in NF1, proteins involved in proliferation and migration in vitro and in vivo. Thus, changes in the expression of AEG-1/AKRIC2/NF1 may be part of the molecular mechanisms through which miR-124-3p reduces proliferation and migration [46][47]. High levels of miR-124-3p also reduce migration, invasion, and EMT in HeLa and C-33A cells through their interaction with AmotL1, an intercellular junction protein that regulates motility and promotes cell migration and invasion. *AmotL1* has been found to be overexpressed in CC [42]. Taken together, all the evidence indicates that miR-124-3p is deregulated in CC and that its target genes are directly involved in malignancy progression.

Data derived from various studies indicate that miR-218-5p also modulates several molecular mechanisms through which it contributes to CC progression. This miRNA is deregulated in CC cell lines and in tissue and, by restoring its expression in SiHa and HeLa cells, it reduces migration, invasion, and EMT through the negative regulation of *SFMBT1* and *DCUN1D1* [44]. miR-218-5p also regulates the expression of *LYN*, a tyrosine kinase that promotes cell growth and survival through the activation of NF-κB; when miR-218-5p decreases the level of *LYN*, migration, invasion, and EMT are reduced and apoptosis is increased in CC cells lines [48]. In a study performed on HeLa cells, the overexpression of miR-218-5p correlated with a decrease in TGF-β, VEGF, IL-6, PGE2, and COX-2, molecules that favor the immune escape of tumor cells. These results suggest that, in women with CC, the significant decrease in miR-218-5p promotes a state of immunosuppression and tumor cell survival. On the other hand, the transcript of the enzyme indoleamine 2,3-dioxygenase 1 (*IDO1*) is a direct target of miR-218-5p and, under conditions that dysregulate this miRNA, the expression of *IDO1* increases, promoting immunological tolerance to tumor cells. Additionally, miR-218-5p promotes apoptosis of HeLa cells by decreasing *survivin*, which negatively regulates caspase-3 [49]. Liang et al. analyzed the expression data of miRNAs obtained by high-throughput sequencing from 251 tissues with CC, registered in the cancer genome atlas (TCGA). They

found that 78 miRNAs were differentially expressed (31 miRNAs were increased and 41 decreased) in CC tissues, with respect to normal tissues. In that study, low levels of miR-145 and miR-218-5p added to high expression of miR-200c predicted a poor prognosis for patients with CC and were significantly associated with average survival. By bioinformatic analysis, the researchers identified the target genes of miR-145, miR-218-5p, and miR-200c and, by using Gene Ontology (GO), found that the target mRNAs of these miRNAs regulate common biological processes. Functional enrichment analysis suggested that miR-145, miR-218-5p, and miR-200c target genes may be involved in several cancer-related pathways, including MAPK, AMPK, focal adhesion, cGMP-PKG, Wnt, and the mTOR signaling pathways [50].

A transcript can be regulated by two or more miRNAs and the evidence indicates that miR-23b-3p, miR-124-3p, and miR-218-5p are functionally related. Zare et al., by bioinformatic analysis, found that, in gastric cancer, miR-124-3p and miR-218-5p regulated the expression of *RUNX2*, a transcription factor whose function contributes to the modulation of cellular proliferation in this malignancy. Thus, *RUNX2* is a direct target of miR-23b-3p and miR-218-5p [51]. Results from independent studies, in ovarian cancer cell lines, also support the role of miR-23b-3p and miR-218-5p in *RUNX2* regulation. Ectopic expression of miR-23b-3p significantly inhibits cell proliferation, migration, and invasion by downregulating *RUNX2* [52]. Additionally, ectopic expression of miR-218-5p inhibits cell proliferation, colony formation, migration, and invasion in vitro and suppresses tumor growth in a tumor-bearing nude mouse model. Conversely, *RUNX2* overexpression rescues ovarian cancer cells from the suppressive effect of miR-218-5p, inducing proliferation, colony formation, migration, and invasion [53]. Thus, miR-23b-3p and miR-218-5p regulate the progression of ovarian cancer, in part, by repressing *RUNX2*. Other studies have also reported *RUNX2* as a direct target of miR-23b-3p [54], miR-124-3p [55], and miR-218-5p [56] in different types of cancer. The data described suggest that miR-23b-3p, miR-124-3p, and miR-218-5p converge in the regulation of cellular processes that contribute to the maintenance and progression of CC, through the regulation of specific targets of each miRNA and through target mRNAs shared by the three miRNAs. Thus, the function of miR-23b-3p, miR-124-3p, and miR-218-5p can have additive or synergistic effects on the modulation of gene expression and activation of signaling pathways, and, consequently, on the regulation of cellular processes recognized as cancer hallmarks. On one hand, it is known that one miRNA post-transcriptionally regulates more than 100 genes directly [57] and that this number increases by indirect regulation; on the other hand, an mRNA can be regulated by two or more miRNAs. Currently, there are few confirmed target mRNAs for miR-124-3p, miR-23b-3p, and miR-218-5p, and few proven target transcripts for two of these miRNAs, however, there are no studies that corroborate targets common to the three miRNAs in CC. Current bioinformatic tools can help explore these aspects.

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