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MiRNAs in Cervical Cancer Radio- and Chemotherapy Response

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Abstract

Cervical cancer (CC) is a very frequent women disease with high mortality and morbidity incidence worldwide, being the developing countries the most affected. Persistent infection with an oncogenic high-risk human papillomavirus (HPV) type is the primary cause of cervical cancer, but other etiologies are needed for complete malignancy such as patient immune response, genetic, and cellular factors, and/or environment. Radiotherapy in combination with cisplatin is the standard treatment for invasive cervical cancer. Nevertheless, this conventional treatment is restricted due to eventual development of drug resistance and systemic toxicity. MicroRNAs (miRNAs) are small non-coding RNAs that regulate the expression of protein-coding genes involved in various cellular processes including cancer where they play a very important role in the development and progression of malignancy. As part of this complex disease, miRNAs have been implicated in the process of drug and radiation resistance and sensitivity. Recent studies have been directed to understand how miRNAs under or over-expressed are determinants of clinical response, and other studies have focused to clarify how the process of radio and/or chemotherapy affects miRNA expression. These works could lead to the design of safer and more effective therapy approaches based on miRNA expression and their target regulation.

Keywords: cervical cancer, miRNAs, chemotherapy, radiotherapy

1. Introduction

Cervical cancer (CC) is the third most common malignancy disease worldwide and has the second place in underdeveloped countries [1]. Persistent infection with an oncogenic high-risk

human papillomavirus (HPV) is the primary cause of cervical cancer [2], being HR-HPV types 16 and 18 responsible of 95% of cases. However, additional etiologies are needed for complete malignancy to be achieved such as patient immune response, genetic, environmental and/or socioeconomical factors [3, 4]. HPV persistent cell infection could give the opportunity to HPV genome integration [5], which commonly results in viral E2 regulator loss leading to E6 and E7 viral proteins constitutive expression allowing development of dysplasia and malignity [6]. Importantly, HPV integration is frequently found near microRNAs (miRNAs), a type of non-coding RNA genes involved in coding genes post-transcription silencing [7], affecting miRNA expression [8]. Aberrant miRNAs expression has been documented for carcinogenesis development in cervical cancer and several other cancer types [9]. Additionally, miRNA processing machinery misregulation is implicated in carcinogenesis, suggesting that they regulate fundamental processes in cancer progression [10].

Concurrent cisplatin-based chemotherapy added to radiation therapy is the standard treatment for advanced CC. It has been demonstrated that chemotherapy and radiotherapy improve survival rates compared to therapy based on radiation alone or combined hysterectomy and radiation. Although a good response to conventional treatment is achieved by some patients, several global meta-analyses in developed and developing countries have shown that CC patients receiving radiotherapy alone or in combination with different chemotherapeutic agents have at 5 years an overall survival rate from 40 to 70% [11–14]. Additionally, systemic toxicity and side effects are a major problem that patients present during treatment [15]. Therefore, much effort is being made in developing safer and more effective treatment alternatives like natural compounds adjuvants [16–18]. Cisplatin and radiation mechanism of action include damage to DNA and induction of DNA damage response (DDR) that consists of the action of a plethora of genes involved in DNA damage repair. The DDR constitutes the action of detectors of DNA damage, signal transducers and effectors that upon effective action of the DDR proteins the cell will be lead either to survival or apoptosis mechanisms depending on DNA damage severity [19–23]. MiRNAs are active modulators of the DDR mechanisms and have been shown as promoters or inhibitors of radio- and chemosensitivity [24–28]. Additionally, the miRNA response to natural compounds has also been evaluated with respect to treatment resistance and sensitivity [29, 30]. Thus, miRNAs have a clear participation in chemo and radio resistance and sensitivity implying a high potential in gene therapy, prognosis and diagnosis.

2. Cervical cancer etiology

The human papillomavirus (HPV) infection is a common sexual transmission infection associated with cervical intraepithelial neoplasia (CIN) 1, 2, 3, and cervical cancer. More than 80% of women are infected during their life while a just a minority develops malignancy disease [31]. Even though HPV elimination is spontaneous, its persistent cell infection could give the opportunity to HPV genome integration [5] allowing development of dysplasia and malignity [6]. HPV infects mucosa and cutaneous surfaces via cell membrane heparan sulfate proteoglycan [32]. HPV replication is exclusive of the squamous stratified epithelium like epidermis or mucosa membranes of cervix [33]. The genes of HPV are classified in early

(E1, E2, E4, E5, E6, and E7) and late (L1 and L2). The formers are implicated in viral genome replication and transcription, while the latest ones constitute structural virus proteins [34].

Viral genome transcription is dependent on cellular differentiation, specific proteins and RNA profile [35, 36]. Upon HPV infection, viral proteins modify normal cell processes. E4 is related to the delivery of HPV copies from the cell, while E5 is allied in apoptosis resistance [37]. Interaction of E6 with p53 via E6-BP conduces to p53-null phenotype [33, 38] disturbing cell cycle and death [39]. On the other hand, E7 interacts with several proteins to boost G1 to S transition [40–42] permitting cell proliferation, enhancing cancer features [43]. The main cell circuit affected by E7 expression is E2F-Retinoblastoma (E2F-Rb). This oncoprotein binds to Rb liberating E2F transcription factor, promoting the transcription of C-MYC, DNA polymerases, cyclins and CdKs among others [40]. During HPV infection, E2 represses E6 and E7 permitting cell proliferation and differentiation recover. However, in most cervical tumors, E2 is lost during the viral genome integration in the cellular genome allowing, E6 and E7 constitutive expression [6]. It is important to mention that HPV integration is frequently found near miRNA genes [7] affecting miRNA expression [8] and probably some other non-coding RNAs. As it will be mentioned later on, non-coding RNAs, especially micro-RNAs (miRNAs), are important genes in which misregulation is closely linked to cancer development, and therefore, HPV integration is crucial for cervical cancer development [8].

3. MicroRNAs in cervical cancer

MicroRNAs are small non-coding genes that exert their function by silencing of coding genes in almost every cellular process, like, cell proliferation, apoptosis, differentiation, migration, invasion, immune response, and metabolism. Before miRNAs maturation, pri-miRNAs and pre-miRNAs are sequentially spliced by Drosha and Dicer proteins, respectively, generating a mature 22–24 nucleotides (nt)-long double strand. To perform mRNA silence mature, miRNAs are incorporated into risk silencing complex, and one miRNA strand is lead to base pair to target mRNA [44]. Then, mRNA is degraded after perfect hybridization is achieved or protein translation is inhibited in incomplete base pair hybridization. Aberrant miRNAs expression has been documented for several carcinomas such as breast, cervical, lung, kidney and colon carcinomas among many others [9], and it has been evaluated by microarray, sequencing, northern blotting, cloning, and reverse transcription-polymerase chain reaction (RT-PCR) techniques [45, 46]. Pioneer study relating miRNAs and cervical cancer was made in 2007. In this chapter, they sequenced 166 miRNAs comparing normal tissue, cell lines and tumor tissues, founding six miRNAs with differential expressions. MiR-21 was over-expressed in cell lines and tumor tissue compared with normal tissue, while let-7b, let7-c, miR-23b, miR-143, and miR-196b expressions were reduced [47]. Since then, many studies have addressed the importance of microRNAs in cervical cancer. Confirmation of various works has provided very useful miRNA expression information to study more profoundly the function and application of this miRNAs in cancer therapy, prognosis, and diagnosis. For example, miR-218 has been found down-regulated in cervical cancer tissue, and its low expression has been related to cancer progression, while its up-regulation in Hela cells has shown that it improves cisplatin

sensitivity [48–51]. In silico and in vitro studies have shown that miRNAs can potentially regulate more than 100 genes, suggesting a great potential for coding genes regulation in cancer cells [52].

4. Cervical cancer therapy

Concurrent cisplatin-based chemotherapy added to radiation therapy is the standard treatment for locally advanced CC (LACC). It has been demonstrated that chemotherapy and radiotherapy improve survival rates compared to therapy based on radiation alone or combined hysterectomy and radiation. In addition, randomized trials demonstrated improved treatment outcome with combinations of cisplatin and 5-fluorouracil compared with radiation therapy alone. It is established that concurrent chemotherapy increases the severity of acute side effects; however, it does not appear to increase the risk of late side effects of radiotherapy. Although a good response to conventional treatment is achieved by some patients, LACC patients treated with radiotherapy have in general a 50% chance of recurrence or persistent disease. Moreover, several global meta-analyses, including patients treated in developed and developing countries, have shown that CC patients receiving radiotherapy alone or in combination with different chemotherapeutic agents have at 5 years an overall survival rate from 40 to 70% [11–13]. This conventional treatment is restricted due to eventual development of drug resistance and systemic toxicity; therefore, much effort is being made in developing safer and effective alternatives like natural compounds as anti-cancer drugs [16–18].

Other approaches have been made toward developing cisplatin analogues with improved chemotherapeutic efficacy and reduced toxic side effects, the most notable of these being carboplatin and oxaliplatin clinically registered [53]. Individual trials have suggested that other drugs, including mitomycin and epirubicin, might be beneficial [54]. It has been investigated the administration of neoadjuvant chemotherapy (NAC), which includes cisplatin, paclitaxel, and carboplatin after radiation therapy enhancing the treatment response [55]. Although the evidence for benefit of concurrent chemotherapy is strong for newly diagnosed, loco-regionally advanced cervical cancers confined to the pelvis, the relative benefits and risks are not well understood for patients who require larger fields of radiotherapy [54]. Many studies are currently being made to improve CC cancer treatment for a major patient percent recovery and less side effects by different approaches as miRNA-based therapy.

5. Cisplatin action mechanism

DNA is vulnerable to damage that originates from endogenous metabolites, such as macrophages and neutrophils produced reactive oxygen species (ROS), reactive nitrogen species (RNS) [56] and exogenous agents including smoking, chemical carcinogens, radiation [57], and genotoxic cancer therapeutics [58]. For instance, cisplatin, cis-diamminedichloroplatinum

(II) $(\text{NH}_3)_2\text{PtCl}_2$ is a DNA-damaging agent used extensively as a chemotherapeutic drug. Particularly, it is successfully employed to treat different cancer types like ovarian and testicular carcinomas, as well as a range of other solid tumors [59, 60]. However, dose-limiting toxic side effects and the occurrence of both acquired and intrinsic drug resistance in cells impose great limitations on cisplatin chemotherapy [61–63].

A hallmark of cisplatin toxicity is loss of outer hair-cells (OHCs) beginning from the cochlear base. A recent study suggests additionally the involvement of stria vascularis and spiral ganglion [64]. One-third of cisplatin-treated cancer patients develop irreversible hearing loss [15]. It has been demonstrated that the toxic side effects of cisplatin depend on the drug cell transportation via the copper transporter CTR1, previously implicated in cisplatin-induced nephrotoxicity [65, 66] or the organic cation transporter OCT2. Upon partial solvolization, cisplatin forms $[(\text{NH}_3)_2\text{PtCl}(\text{H}_2\text{O})] + (\text{monoqua complex})$, which can be transported by OC.

Although cisplatin detailed mechanism of action is presently unclear, it is generally thought that the covalent binding of cisplatin to cellular DNA and subsequent formation of bulky platinum-DNA (Pt-DNA) adducts mediates the cytotoxicity of this anti-cancer agent [67, 68]. Intra-strand DNA cross-links are the most common adducts formed, although inter-strand DNA cross-links and DNA-protein cross-links can also occur [69, 70]. The intra-strand DNA lesions preferentially form between the N-7 of adjacent guanine residues, inhibiting the passage of polymerases and thus interfering with DNA replication and RNA transcription inside target cells [71–74].

The active response to cisplatin induces DNA damage entailing two key processes. (1) Repair of DNA damage through the removal of cisplatin adducts and (2) induction of cell death via apoptosis when repair cannot be carried out successfully. Among these DNA repair pathways, NER repairs damaged DNA commonly caused by chemotherapeutics such as platinum drugs, which has been proven to be associated with chemotherapy resistance in non-small cell lung cancer (NSCLC) [19].

Cisplatin's mechanism of action in addition to cell cycle arrest and apoptosis includes cellular senescence through activation of onco-suppressing p53 and p16 proteins, and there is strong evidence that p53 plays a role in cisplatin sensitivity [75]. Transcription factor NFκB and the serine/threonine kinase Akt play critical roles in cancer cell survival and have been shown to be activated in various malignancies [76]. Thus, efforts are underway to identify alternate therapies, including the use of curcumin in combination with radiation and/or chemotherapeutic drugs in hepatic, ovarian, and head and neck squamous cell cancer HNSCC [77–79]. It is believed that the therapeutic potential of cisplatin will be enhanced with the addition of curcumin, with lower, less toxic doses of cisplatin required for its cytotoxic effect [30].

6. Ionizing radiation action mechanism

Ionizing radiation is a type of high-energy radiation that in contact with atoms and molecules releases electrons generating ions that can break covalent bonds. Ionizing radiation directly

affects DNA structure by inducing DNA breaks, particularly double-strand breaks (DSBs). Secondary effects are the generation of reactive oxygen species (ROS) that oxidize proteins and lipids and induce several damages to DNA like generation of a basic sites and single-strand breaks (SSBs). Quiescent and slowly dividing cells are less radiosensitive, like those constituting the nervous system, while cells with high proliferation rates are more radiosensitive, like bone marrow, skin, and epithelial cells of the gastro-intestinal tract, among others. Ionizing radiation can be divided into X-rays, gamma rays, alpha, and beta particles, and neutrons. The radiation dose is measured in gray (Gy) units, a measure of the amount of radiation absorbed by 1 kg of tissue [20].

Radiotherapy is a treatment aimed at shrinking the tumor mass or at eliminating residual tumor cells by exposing the tumor to ionizing radiation. Radiotherapy regimes mostly use X- and gamma radiation and affect tumor and healthy irradiated cells indistinctly [80].

Ionizing radiation causes DSBs directly, and reactive oxygen species (ROS) caused by radiation also indirectly damages DNA. ROS generate apurinic/apyrimidinic (abasic) sites in the DNA, SSBs, sugar moiety modifications, and deaminated adducted bases [81, 82]. After DNA damage, the cell repair machinery is activated and stops the cell cycle at specific control checkpoints to prevent continuation of the cycle and repair damaged DNA. If tumor cells can efficiently repair the radiation damage, resistance to radiation develops, enabling cells to survive and replicate. If the damage remains unrepaired, these mechanisms induce programmed cell death or apoptosis to prevent accumulation of mutations in daughter cells [83, 84]. Ionizing radiation unavoidably spreads to normal tissue, inducing side effects in tumor-adjacent normal cells that may contribute to chromosomal aberrations and to increase the risk for new malignancies. Therefore, reduced patients survival could be a consequence of high radiation doses administration [21].

Individual radiation treatment based on DSB repair capability could predict toxicity to surrounding tissues, thereby improving treatment safety. DSB repair capability depends not just on gene integrity, but also on gene expression. For example, genetic and epigenetic mechanisms may reduce or abrogate the expression of genes involved in DSB repair [85]. DNA repair is orchestrated by a series of pathways, mainly including nucleotide excision repair (NER), base excision repair (BER), DNA mismatch repair (MMR), and single-strand break repair (SSBs) [86]. DSB repair is achieved in three ways: non-homologous end joining (NHEJ), conservative homologous recombination (HR), and single-strand alignment (SSA), also called non-conservative homologous recombination [87].

Three interconnected sensor systems have been described that have the ability to detect a single DSB within minutes after its formation [88]: (1) PI3K-related kinases (PIKKs), (2) ataxia telangiectasia and Rad3-related (ATR), ataxia telangiectasia mutated (ATM) and (3) DNA-dependent protein kinase (DNA-PK). ATR participates in the recognition of SSBs induced by cisplatin or IR, whereas ATM is essentially implicated DSBs recognition. Importantly, damage signals are transduced to the cell, while cells react to decide to either repair damaged DNA or activate cell cycle checkpoints or induce apoptosis. Upon DSBs induced by cisplatin and/or radiation, as a transducer, the targets of ATM/ATR with dual-functions promote survival or cell death. Meanwhile, cell signaling pathways activate cell cycle checkpoint halting

its progression proving time to cells to repair the damage by the recruitment of DNA repair proteins to facilitate DSB repair triggered by NHEJ or HR, depending on the cell cycle phase [22]. If DNA damage is greater than the repair capacity, hence replication and transcription will be blocked, and DDR signals activate downstream cell death pathways. Importantly, DNA repair genes are actively regulated by miRNAs, which are highly found misregulated in cervical cancer and have marked effect on chemo- and radiotherapy resistance, implying a big target potential in gene therapy.

7. MiRNAs in mechanisms of cancer therapy resistance

Some studies have enlightened miRNAs contribution to chemo- and radiotherapy response; for example, it was shown that cisplatin, paclitaxel, and carboplatin prior to laparoscopic radical hysterectomy (LRH) improved patient response by inducing p53, miR-34a, and miR-605 expression, while levels of E2F1 and Mdm2 were significantly low [55]. Additionally, alternative less toxic natural compounds are analyzed; for example, it was shown that I'5-I' acetoxichavicol acetate (ACA) induced comparable levels of dose- and time-dependent cytotoxicity on a variety of tumor cell lines to current commercial anticancer drugs, without any adverse effects on normal cells [29]. A total of 25 miRNAs were found to be expressed significantly different in response to ACA and/or cisplatin including has-miR-138, has-miR-210, has-miR-744 which target genes involved in apoptosis and cell cycle progression regulating pathways [89].

Genotoxic agents, such as UV light, γ -irradiation, oxidative stress, and chemical mutagens, induce a DDR that results in the up- and down-regulation of miRNAs expression levels that will happen in a few hours after DNA damage and will return to basal levels in 24 h. MiRNA DDR seems to be influenced by type of damaging agent, radiation Gy dose and time of exposure as well as cell type involved [90–94]. MiRNA-induced response has been documented as transcriptionally modulated miRNA expression and biogenesis modulation miRNA maturation.

In response to DNA damage, the ATM or ATR kinase activates p53, which in turn transactivates genes involved in cell cycle regulation, senescence, and apoptosis. A clear example is the transactivation of miRNA-34 family by p53 upon DNA damage and oncogenic stress [95]. MiR-34a ectopic expression leads to G1 phase cell cycle arrest in both primary and tumor-derived cell lines likely through silencing a program of genes that promote cell cycle progression. In addition to the miR-34 family, miR-192, miR-194, miR-215, and miR-17-92 cluster are other miRNAs found to be transcriptionally regulated by p53. In addition, other DNA damage responsive transcription factors, such as NF- κ B, c-Myc, CREB and E2F1, modulate miRNA expression [96, 97]. However, the specific functions of those miRNAs in DNA damage need further study.

MiRNAs involvement in DDR seems to be additionally modulated beyond transcription regulation by transcription factors through post-transcription modulation. Miyazono group's

study demonstrated that several miRNAs, including miR-16-1, miR-143 and miR-145, were post-transcriptionally up-regulated in a p53-dependent and p68/p72-dependent manner upon genotoxic stress [98, 99]. In colorectal HCT116 and lung WI-38 cell lines, p53 interacts with the Drosha processing complex through direct interaction with p68 and, in turn, facilitates the processing of pri-miRNAs to pre-miRNAs. Apparently, the guardians of genome, p53/p63/p73, modulate the processing of a group of miRNAs, including the tumor suppressor miRNAs, let-7, miR-34, miR-15/16a, miR-145, miR-26, miR-29, and miR-146a [100]. Another protein modulating miRNA processing is KSRP, a KH type splicing ribonucleoprotein that serves as a critical component of both Drosha and Dicer complexes and regulates the biogenesis of a subset of miRNAs like miR-16 and miR-143 and miR-145 by Drosha and Dicer respectively [101].

As a response to DNA damage, a novel class of small RNAs, named DDR-regulating RNAs (DDRNs), has been identified near double-strand breaks (DSB) [102]. It has also been reported the presence of Dicer-dependent small RNAs (named DSB-induced RNAs, diRNAs) arising from the sequences flanking DSBs in plants and in human cells [103]. At the moment how do these site-specific small RNAs act to control DDR activation, it is not clear; however, it seems that the presence of DSB-derived site-specific small RNAs may be a universal phenomenon in DNA damage, involved in recruitment of chromatin-modifying complexes to sites of damage or guiding DNA repair signaling [104].

MiRNAs are also involved in mechanisms of multidrug resistance (MDR) like dysregulation of drugs transporters, defects of apoptosis and autophagy machinery, alterations of drug metabolism and drug targets, and disruption of redox homeostasis [28]. Some miRNAs regulating drug transporters like (P-gp/ABCB)1 are miR-451, miR-27a [105–108], miR-138 [109], miR-298 [110], miR-381, and miR-495 [111]. The entire process of autophagy, including autophagic induction, vesicle nucleation, vesicle elongation, and completion, can be modulated by different miRNAs [28]. Some miRNAs documented in this cellular process are miR-30a [112], miR-30d [113], miR-204 [114], miR-16 and miR-17 [115, 116], miR-200b, miR-15a [116], and miR-181a [117]. Metabolic regulation by miRNAs has been documented for miR-27b, which can modulate resistance to docetaxel in cancerous cells [118, 119] and sensitizes cancer cells to a broad spectrum of anti-cancer drugs in vitro and in vivo by activating P53-dependent apoptosis and reducing CYP1B1-mediated drug detoxification [120], and for miR-892a that targets CYP1A1 [121]. Apparently, miRNAs can impact anti-cancer drugs sensitivity by modulating the expression of drug targets. For example, miR-192 and miR-215 may influence 5-FU sensitivity by targeting Tynidilate synthetase (TS) enzyme in colorectal cancer cells [122], while miR-211 can increase the sensitivity of pancreatic cancer cells to gemcitabine [123], and let-7 negatively regulates RRM2 expression and sensitizes PDAC cells to gemcitabine [28].

8. MicroRNAs in cervical cancer chemo- and radiotherapy resistance

Additionally to several works involving coding genes, other efforts involving miRNAs are being made for the understanding of cellular chemo- and radiosensitivity. In this context, it

has been shown that miRNAs expression is affected in radio and chemo-resistant cells [25–28]. Some miRNAs have been identified as promoters of radioresistance such as miR-421, which regulates the activity of DNA repair ATM protein [124]; miR-23b and miR-34a, which are regulated by p53 protein [125]; miR-106b, which silences cell cycle regulator protein p21 and promotes cell cycle progression and overrides a doxorubicin-induced DNA damage checkpoint and miR-17-92 cluster [126, 127]; while others have been found as radiosensitizers such as miR-424 promoting radiosensitivity by targeting aprataxin, which stimulates DNA repair and protects cells against genotoxic stress in cancer cells [128] and miR-375 promoting radiosensitivity of HR-HPV-positive cervical cancer cells by targeting the ubiquitin ligase mRNA (UBE3A) leading to decreased p53 degradation and thereby increasing radiation-induced apoptosis [129]. Interestingly, miR-375 was also found increased in acquired paclitaxel resistance in cervical cancer [130].

Some studies have shown that miRNAs involved in chemosensitivity promotion. For instance, the sensitivity to cisplatin is augmented via miR-181a Protein Kinase C Delta (PRKCD) silencing [131] and miR-218, which also impairs tumor growth and induces apoptosis via AKT-mTOR pathway in HeLa cells [50]. Additionally, miR-218 enhances Rapamycin sensitivity by mTOR pathway Rictor targeting [132]. An study showed that p53:miR-34a:E2F1 and p53:miR-605:Mdm2 are activated after chemotherapy with cisplatin, paclitaxel, and carboplatin cycles improving the treatment response of cervical cancer patients [55]. Other cisplatin sensitizing miRNAs are miR-15b and miR-16 that target Bcl2 in Hela cells [133], while miR-15a and miR-16 induce autophagy and sensitize cells to camptothecin [116]. Other miRNAs promote chemosensitivity to other drugs, for example, miR-126 additionally to hinder proliferation it enhances sensitivity to bleomycin [134]; miR-125a, promotes paclitaxel sensitivity via silencing of signal transducer and activator of transcription (STAT3) [135], and miR-145 that is regulated by p53 influences sensitivity to mitomycin and reverses the chemoresistance induced by glucocorticoids [136].

Recent works have focused on the design of radio and chemotherapy response predictors. Pedroza-Torres and cols identified a miRNA expression signature based on the over-expression of seven miRNAs (miR-31-3p, miR-3676, miR-125a-5p, miR-100-5p, miR-125b-5p, miR-200a-5p, and miR-342) to identify CC patients who could fail to conventional, treatment based on chemo- and radiotherapy [137]. Other works have provided similar valuable information, for example, miR-200a and miR-9 signature could predict patient survival. Particularly, miR-200a could affect the metastatic potential of cancer cells by negatively regulating cell motility genes [138]. Another study indicated that the miRNA signature consisting of miR-630, miR-1246, miR-1290, and miR-3138 could promote radio resistance of CC cells [138–140].

A total of 25 miRNAs were found to be differentially expressed in response to 1S-1-acetoxychavicol acetate (ACA) and/or cisplatin. MiR-138, miR-210, and miR-744 have predicted gene targets involved in signaling pathways regulating apoptosis and cell cycle progression. Remarkable, ACA acts as a chemosensitizer that synergistically potentiates the cytotoxic effect of cisplatin in cervical cancer cells. MiRNA expression changes with the administration of ACA and/or cisplatin suggests that miRNAs play an important role in anticancer drug responses making them ideal for therapeutic treatment of patients with chemoresistance [89].

Curcumin (Cur) is a phenolic compound purified from the rhizome of *Curcuma longa*, historically used in traditional medicine [141, 142]. It has been reported that Cur reduces the expression and function of P-glycoprotein (P-gp), a protein highly expressed in tumoral cells [143]. This natural compound and derivatives have been catalogued as not toxic in humans even at high doses (12 g/day) [144]. Cur efficacy is limited due to the low level of oral bioavailability, poor absorption ability, a high metabolic rate, inactivity of metabolic products, rapid elimination and clearance from the body, poor pharmacokinetics and solubility, and degradation under natural to basic pH conditions. Conjugation of Cur to nanoparticles (NPs) and anti-P-glycoprotein (P-gp) antibody (Cur-NPs-APgp) targeting to P-gp could enhance paclitaxel (PTX) sensitivity both in vitro and in vivo [140]. Curcumin reverses cisplatin resistance in SiHa-resistant phenotype (SiHaR) cells by overcoming over-expression of multidrug resistance protein 1 (MRP1) and Pgp1 and sensitized cervical cancer cells toward cisplatin-induced cell killing with lower chemotherapeutic drug dose [145]. Recent evidence has suggested curcumin-induced modulation of the expression of several miRNAs such as suppression of oncomiRs miR-21, miR-17-5p, miR-20a, and miR-27a and over-expression of miR-34 a/c and epithelial-mesenchymal transition-suppressor miRNAs among the most important effects of curcumin on miRNA homeostasis [24].

Other natural compounds with anticancer potential are *Cratoxylum formosum* subsp. *pruniflorum* (Kurz.) Gogel. (Teawdang) phenolic extracts that could inhibit growth of HeLa and SiHa cancer cell lines [146]. Teawdang is a northeast Thai vegetable that contains several bioactive constituents especially chlorogenic acid which has radical scavenging activity [147]. Thus, miRNA regulation investigation of these bioactive compounds is recommended. It could be very supportive the study of miRNA response to other natural compounds with anticancer potential and drug resistance overcome like Chrysin from Thai propolis [148]; a series of ferrocene and (arene)ruthenium(II) complexes attached to the naturally occurring anticancer naphthoquinones plumbagin and juglone [149]; sesquiterpene lactones isolated from *Illicium simonsii* [150]; phenanthroindolizidine alkaloids, (-)-(R)-13a α -antofine (1) and (-)-(R)-13a α -6-O-desmethylanofine (2) and natural products, (-)-(R)-13a α -secoantofine (3) and (-)-(R)-13a α -6-O-desmethylsecoantofine isolated from *Cynanchum vincetoxicum* [151].

9. Conclusions and considerations

In the present literature, it is reviewed, analyzed, and organized novel information regarding miRNAs involved in resistance to drugs, natural compounds and radiation in cervical cancer treatment. The present data could encourage future research to generate optimal treatment strategies for individual patients especially before the course of chemo- and radiotherapy based on miRNAs regulation, conventional and non-conventional cervical cancer therapy.

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