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The Amphibolous Role of miR-203 in Gastrointestinal and Urogenital Cancers

Lei Zhan, Bing Wei*

Department of Gynecology and Obstetrics, The Second Affiliated Hospital of Anhui Medical University, Hefei, China

Email address:
m1351565@163.com (Bing Wei)
*Corresponding author

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Abstract: miR-203, as a member of the miRNAs family, play a major role in control of gene expression during normal development and are disrupted in the initiation and progression of specific diseases. It was worth nothing that a growing body of evidence indicated an abnormal expression of miR-203 in several human leading cancers including gastrointestinal and urogenital cancers. The cytosine-phosphoguanine (CpG)-island methylation was one of the most significant factors which controlled the expression of miR-203. Furthermore, miR-203 participated in these cancers *via* targeting its downstream genes. However, the precise regulatory mechanisms underlying miR-203 association with these cancers are still not fully understood. The aim of this review is to sum up the collective knowledge of miR-203 in gastrointestinal and urogenital cancers.

Keywords: miR-203, Gastrointestinal Cancers, Urogenital Cancers, Methylation, Targeting

1. Introduction

miRNAs are known as one of the most popular epigenetic genes, are a class of small noncoding RNAs of about 22 nucleotides in length [1]. miRNAs were first identified in nematodes in 2001 [2]. It was investigated that miRNAs regulated protein expression at the post-transcriptional level through binding to mainly the 3'-untranslated region (UTR) of messenger RNAs (mRNAs), which terminated in mRNA translational repression or degradation or both [3-5]. Since the first miRNA was recognized, more than 2000 miRNAs have been identified and shown to regulate nearly one-third of the genes in the human genome [6]. As key regulators of post-transcription in diverse array of cells, these miRNAs are naturally involved in a wide variety of biological processes and serve as potentially diagnostic or prognostic biomarkers in cancers [7-9]. Methylation is also an important form of epigenetic modification, which refers to change of genes expression caused by addition of a methyl group to the 5′position of cytosine residues in the (CpG) dinucleotide [10]. Methylation is a ubiquitous appearance in the development of cancers [10]. It was worth mentioned that the expression of miRNAs could be regulated by CpG-island methylation [10, 11].

miR-203 is a 22-nt non-coding RNA in miRNAs family and was initially found to be specifically expressed in keratinocytes [12]. In recent years, accumulating studies showed that miR-203 played essential roles in determining the development of cancers. Simultaneously, the expression of miR-203 in cancers could be regulated by CpG-island methylation. For example, CpG-island methylation-mediated miR-203 down-regulation was implicated in HCC progression by protecting survivin protein, while over-expression of miR-203 significantly suppressed proliferation of HepG2 cells, suggesting miR-203 acted as a tumor suppressor in HCC [13]. Interestingly, it was illustrated that the level of miR-203 was up or down in breast cancer compared to the normal group, the promoter methylation-caused miR-203 down-regulation contributed to breast cancer development by up-regulating snail homolojg 2 (SNAI2 or Slug) level [14]. In contrast, the study on the mechanism of miR-203 up-regulation in cancers was scarce. But in ovarian tumor, miR-203 up-regulation was attributable to hypomethylation [15, 16]. These findings prompted that miR-203 was an intricate regulator in cancers. However, the regulatory mechanisms of miR-203 in these certain cancers are still unclear and need to be further detected. In this review, we will focus to sum up the recent advances of miR-203 in a wide diversity of human leading cancers including gastrointestinal and urogenital cancers.

2. miR-203 and Gastrointestinal Cancers

2.1. miR-203 and HCC

HCC is one of the most lethal cancers and ranks the third leading cause of cancer-related deaths every year worldwide [17]. miR-203 was first detected with a decreased level in benign tumors compared to non-tumorous liver tissue [18]. Subsequent study demonstrated that that miR-203 showed frequent tumor-specific methylation in primary tumors of HCC with paired non-tumorous liver tissues. Promoting the expression of miR-203 led to inhibition of HCC cells growth *via* suppressing ATP binding cassette, subfamily E, member 1 (ABCE1), cyclin-dependent kinase 6 (CDK6) and survivin expressions [19]. These results convincingly implied that the low level of miR-203 was caused by CpG-island methylation and miR-203 acted as a tumor suppressor in HCC. In line therewith, a recent study revealed that miR-203 expression was lower in tumor tissues of patients with post-liver transplantation (LT) HCC recurrence than those in patients with non-recurrence, higher miR-203 expression predicted a significantly better recurrence-free survival (RFS) and overall survival (OS) [20]. Furthermore, Liu and colleagues noted that the expression of miR-203 was negatively correlated to metastasis, clinical tumor nodes metastasis (TNM) stage, nm23 expression, p21 expression, microvessel density (MVD) and was positively correlated to cirrhosis in HCC [21]. Additionally, recent studies implicated miR-203 as a potential therapeutic target based on the findings that down-regulation of miR-203 in HCC was closely linked to advanced clinical features and poor OS, and over-expression of miR-203 could suppress the proliferation and metastasis of HCC by down-regulating oncogene human A disintegrin and metalloprotease9 (ADAM9), oncogenic long non-coding RNA HULC, enhancer of zeste homolog2 (EZH2) and Bmi-1 [22, 23]. In the meanwhile, the over-expression of miR-203 and down-regulation of EZH2 and Bmi-1 in HCC cell line Hep3B may form a regulatory axis (EZH2-Bmi-1-miR-203) to regulate cell proliferation and invasion [23]. In addition to methylation-mediated miR-203 reduction in HCC, miR-203 could also be attenuated by the over-expression of hepatitis C virus (HCV) core protein, which was associated with epithelial to mesenchymal transition (EMT) and of HCC progression [24].

2.2. miR-203 and Stomach Cancer

Stomach cancer or gastric cancer is the fourth commonly diagnosed cancer worldwide, Eastern Asia, Eastern Europe and South America are the high-incidence areas [25]. miR-203 expression was proved to be correlated with tumor size and macroscopic type in gastric cancer tissues. Lower level of miR-203 concluded increase tumor sizes in patients with gastric cancer. Furthermore, ectopic expression of miR-203 resulted in obviously growth arrest in human gastric cancer cell lines (SGC-7901) compared to normal gastric epithelial cell line [26]. In consistent with these results, in the side population (SP) cells of the gastric cancer cell line MKN-45, Zhang and colleagues also found miR-203 was down-regulated [27]. A plethora of reports demonstrated that miR-203 was silenced through CpG-island methylation in gastric carcinoma or gastric lymphomagenesis [28, 29]. Craig et al. showed that epigenetic silencing of microRNA-203 induced its target gene ABL1 expression and contributed to Helicobacter-associated gastric lymphomagenesis, treatment of lymphoma B cells with demethylating agents led to increased miR-203 expression and decreased of ABL1 expression [28]. Du et al. revealed an inverse relationship between the CpG-island methylation and level of miR-203, which was considered to be an adaptation to the development of gastric carcinoma [29]. Recently, miR-203 was shown to be aberrantly down-regulated in H. pylori positive gastric cancer tissues and cells, over-expression miR-203 could inhibit growth and invasion of gastric cancer cells by inhibiting calcium/calmodulin-dependent serine protein kinase (CASK) expression [30]. Furthermore, Shi et al. evaluated that improved the level of miR-203 could restrict cells metastasis *via* targeting Slug in Slug-mediated stomach cancer [31]. Most important, serum miR-203 was suggested to serve as a noninvasive biomarker for prognosis and to predict metastasis in gastric cancer patients with the finding that lower serum miR-203 expression in gastric cancer patients was significantly involved in a higher T stage, vessel invasion, and lymph node, peritoneal, and distant metastases, while low expression of serum miR-203 was significantly associated with poor disease free [32]. Intriguingly, another study demonstrated that miR-203 was specifically up-regulated in gastric adenocarcinoma patients with regular alcohol consumption, suggesting that level of miR-203 was association with lifestyle behaviors of gastric adenocarcinoma patients [33].

2.3. miR-203 and Pancreatic Cancer

Pancreatic cancer is the fourth leading cause of tumor-related deaths with a high recurrence rate in the industrialized world [34]. A recent estimation showed a close connection between miR-203 and pancreatic ductal adenocarcinomas (PDAC), which providing a valuable proof that PDAC patients who expressed higher level of miR-203 may has a poorer overall survival, and a combined over-expression of miR-155, miR-210, miR-222 and miR-203 result in increased risk of tumor-related death, implying that miR-203 may had a tumor-promoting role in PDAC [35]. In line with this, in animal experiment, miR-203 was observed to be highly expressed in the serum of PDAC rats compared to control rats [36]. Based on these findings, subsequent studies highlighted a positive association of miR-203 over-expression with significantly shorter survival time and poor prognosis in pancreatic cancer, indicating miR-203 could act as a prognostic marker in pancreatic cancer patients [37, 38]. Moreover, miR-203 was also found to be significantly over-expressed in pancreatic intraepithelial neoplasms (PanINs) compared with normal pancreatic duct samples [39]. A novel mechanism underlying miR-203 in pancreatic cancer was revealed that miR-203 promoted pancreatic cancer cells

proliferation, migration and invasion by degrading salt-inducible kinase 1 (SIK1) [40]. The above results indicated that miR-203 acted as oncogene in the development of pancreatic cancer. However, Miao and colleagues elucidated miR-203 could inhibit cell migration, invasion and EMT transition in pancreatic cancer, the inhibition role of miR-203 in cell migration and invasion was *via* inhibiting caveolin-1 [41]. Likewise, miR-203 was reported to dampen toll-like receptor 4 (TLR4) and its related genes tumor necrosis factor-α (TNF-α) and interleukin-12 (IL-12) expression in human pancreatic cancer cell line panc-1 [42]. Noteworthily, a recent study illustrated that the HDAC inhibitor mocetinostat could restore miR-203 expression and confer drug sensitivity to the EMT activator ZEB1 in pancreatic cancer cells [43]. These findings suggested that miR-203 also acted as a tumor suppressor in pancreatic cancer. More recently meta-analysis revealed that pancreatic cancer prognostic significance included high expression of miR-203, yet the result was deficient [44].

2.4. miR-203 and Esophageal Cancer

Esophageal cancer, which ranks sixth as the leading cause of cancer mortality, is one of the most common cancers in China [45]. In recent years, emerging evidence about the down-regulation of miR-203 in esophageal cancer has been collected [46-48]. For instance, Feber et al. noted that miR-203 was expressed 2- to 10-fold lower in esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinomas (EAC) than in normal esophageal epithelium [46]. Furthermore, the low level of miR-203 contributed to esophageal cancer was indicated to be associated with transcription factor JunB and ABCE1 over-expression [47]. Till now, it have been extensively studied that miR-203 could inhibit the proliferation, migration and invasion of esophageal carcinoma cells by inhibiting different targets directly [49]. such as ΔNp63 [50, 51], Ran [51, 52], LIM and SH3 protein 1 (LASP1) [52], Bmi-1 [53, 54] and p63 [55]. Of special note is that E2F1 could directly bind to miR-203 promoter region and activate miR-203 transcriptional activity, in response, miR-203 inhibited cell proliferation by down-regulating the expression of cyclin-dependent kinase 6 (CDK6), which resulted in E2F1 release and G1 cell cycle arrest in ESCC [56]. In addition, Li et al. found epidermal growth factor (EGF)-induced C/EBPβ participated in EMT by dampening miR-203 expression in ESCC [57]. These findings suggest miR-203 earns a status of master regulator in esophageal cancer development and may provide new avenues for the diagnosis, prognosis and therapy of this deadly disease.

2.5. miR-203 and Colorectal Cancer

Colorectal cancer (CRC) is the third leading cause of cancer-related deaths worldwide with an estimated 5-year survival rate ranging from 10 to 95% [58]. The incidence of CRC in China is increasing at an alarming rate in recent years [59]. Surgery and chemotherapy are the main option to treat CRC. However, CRC always are detected at later stages and the chemoresistance lead to treatment failure [60]. It was accepted that the down-regulation of miR-203 caused by hyaluronan (HA)/CD44/c-Src/Snail signaling in CRC cell lines contributed to maintenance of CRC cell stemness, Snail directly regulated the expression of miR-203 by binding to the E-box elements of the miR-203 promoter. Over-expression of miR-203 could inhibit the stemness of CRC cell, such as tumor incidence and growth rate [61]. Furthermore, miR-203 was suggested to be closely related with the chemoresistance in CRC, but the results were controversial [62-64]. Chen et al. found over-expressed miR-203 reversed chemoresistance in p53-mutated colon cancer cells through inhibiting Akt2 expression [62]. Gao and colleagues validated that miR-203 could enhance chemosensitivity to 5-fluorouracil by targeting thymidylate synthase (TYMS) directly in colorectal cancer [63]. However, Lu et al. identified that the expression of miR-203 was amplified in oxaliplatin-resistant CRC cell lines, and miR-203 induced oxaliplatin resistance in colorectal cancer cells by negatively regulating ATM kinase, knockdown of miR-203 would sensitize chemoresistant CRC cells to oxaliplatin [64]. In addition, miR-203 could regulate cell proliferation and apoptosis in CRC. For example, over-expression of miR-203 suppressed anti-apoptotic gene Bcl-xL level and facilitated apoptotic proteins Bax and active caspase-3 expressions [62]. miR-203 played a negative role in cell proliferation by inhibiting cell proliferation-related proteins directly, such as Hakai and Zinc finger protein 217 (ZNF217) [65, 66].

3. miR-203 and Urogenital Cancer

3.1. miR-203 and Prostate Cancer

Prostate cancer is the most incident male malignancy and ranks the second leading cause of cancer death in United States men [67]. miR-203 exhibited a tumor-suppressing role in prostate cancer. Low level of miR-203 was observed in prostate carcinoma cell lines compared to normal epithelial prostate cell lines, *in vitro* and *in vivo* studies implicated that re-expression of miR-203 contributed to a negative effect on the tumorigenesis and metastasis of prostate cancer cells partly through inhibiting proliferation and inducing of apoptosis. Furthermore, the authors elucidated that the negative effect of miR-203 on tumorigenesis and metastasis of prostate cancer might derive from its ability to pleiotropically regulate a cohort of genes which involved in metastatic dissemination, such as survivin, ZEB2, Runx2, Dlx5, and smad4, Ras-related protein Rap-1A (Rap1A), LASP1 [68-70]. In addition, Siu and colleagues proposed that increased amphiregulin (AREG), epiregulin (EREG) and transforming growth factor-α (TGFA) expression were related to reduced miR-203 expression in metastatic prostate cancer patients and miR-203 could directly bind to the AREG, EREG, and TGFA and regulate the stability of AREG, EREG, and TGFA mRNA [71]. Recently, it was indicated that miR-130a, miR-203 and miR-205 were down-regulated and jointly directly targeting

the mitogen-activated protein kinase (MAPK) and androgen receptor (AR) signaling pathways which were known as two major oncogenic pathways in prostate carcinoma, reconstitution of miR-130a, miR-203 or miR-205 resulted in increased apoptosis and cell cycle arrest in G1 phase [72]. More recently, Qu et al. reported that miR-182 and miR-203 were completely repressed during EMT. Re-expression of miR-182 and miR-203 induce mesenchymal to epithelial transition (MET) features and growth factor-independent growth by repressing SNAI2 in prostate cells [73]. Remarkably, it was implicated that miR-203 could be a potential biomarker for detection and prognosis of prostate cancer in a recent study [74]. Of special note is that miR-203 was also identified to be up-regulated in prostate secretion samples of prostate cancer patients but the mechanism remains undetermined [75].

3.2. miR-203 and Bladder Cancer

Human bladder cancer is a common cancer affecting the urinary system, and ranks the fourth leading cause in men, and the tenth common in women [76]. miR-203 was firstly verified to be significantly down-regulated in bladder cancer tissues by Bo et al. [77]. Over-expression of miR-203 promoted cells apoptosis and inhibited cells proliferation in bladder cancer cell line by inhibiting oncogene Bcl-w [78]. Furthermore, Saini et al. found miR-203 was frequently down-regulated in bladder cancer because of the promoter DNA hypermethylation. Curcumin directly induced hypomethylation of the miR-203 promoter and up-regulation of miR-203 level, which led to a significant reduction of its target genes Akt2 and Src expression, further inducing the suppression of tumorigenicity in bladder cancer cells [79]. Recently, decreased miR-203 was indicated to predict progression and poor prognosis for bladder cancer patients treated with cisplatin, while over-expression of miR-203 could improve cisplatin sensitization *via* inhibiting Bcl-w and survivin directly [80].

3.3. miR-203 and Breast Cancer

Breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer mortality in women worldwide [81]. It was noted that miR-203 was up-regulated or down-regulated in breast cancer [82, 83]. For example, Ru et al. detected a significant up-regulation of miR-203 expression in human breast cancer tissues as compared to patient-matched non-tumor breast tissues [84]. Cisplatin, an effective drug for treating breast cancer, induced apoptosis protein p53 and Bax expression in miR-203 knockdown breast cancer cells but not in control cells, implicating that knockdown of miR-203 could sensitize breast cancer cells to cisplatin. To further explored the underlying mechanisms by which knockdown of miR-203 string up breast cancer cells to cisplatin, the authors demonstrated that suppressor of cytokine signaling 3 (SOCS3), a directly target of miR-203, could effectively enhance cisplatin-mediated cell cytotoxicity in breast cancer cells [84]. This finding was supported by another study demonstrating that kallistatin, which was a tumor suppressor protein, could reduce miR-203-mediated SOCS3 inhibition by activating PKC-ERK signaling [85]. Furthermore, over-expression of miR-203 could inhibit phospholipase D (PLD) protein expression [82]. which was consistent with the subsequent finding that PLD induction upon starvation led to phosphatidic acid (PA) expression, which induced expression of miRNA-203 that in turn inhibited PLD translation [86]. However, studies also showed that miR-203 was down-regulated in breast cancer cell lines, ectopic expression of miR-203 could inhibit tumor cell proliferation and enhance the sensitivity of chemotherapy by directly targeting baculoviral IAP repeat containing (BIRC5), LASP1, Bmi-1 and Runx2 [87-90]. The down-regulation of miR-203 also led to the loss of post-transcriptional regulation of DNMT3b, which governing the aberrant DNA hypermethylation in breast cancer [91, 92]. Importantly, recent work from Zhang and colleagues found miR-203 was up-regulated in breast cancer primary tumors and nonmetastatic breast cancer cell lines in comparison to noncancerous tissue and immortalized cell lines, and down-regulated in metastatic breast cancer cells, which was caused by promoter hypermethylation. Over-expression of miR-203 led to cells apoptosis and inhibited cell invasion, cell migration and cell cycle in G0/G1 phase by directly down-regulating the SNAI2 [93]. Consequently, miR-203 could be a prognostic miRNA in metastatic breast cancer patients [94].

3.4. miR-203 and Kidney Cancer

The incidence of kidney cancer has increased consistently during the past years, and kidney cancer is the eighth most frequent cancer in Canada [95]. Limited evidence was collected about the relationship between miR-203 and kidney cancer. However, miR-203 was found to be down-regulated in the benign oncocytomas and up-regulated in the malignant chromophobe renal cell carcinomas (RCC) relative to normal kidney [96]. Clearly, there is a need for a deeper mechanistic understanding for the role of miR-203 in kidney cancer, but the initial studies suggest that miR-203 may be a candidate regulator in kidney cancer.

3.5. miR-203 and Cervical Cancer

Cervical cancer, which is a typical gynecological tumor and leading cause of about 300,000 deaths each year, is the third most common type of cancer in women all over the world [81]. Molecular and epidemiological data confirmed that high-risk human papillomaviruses (HPV) are a major etiological agent of cervical cancer [81]. miR-203 was detected to be down-regulated in cervical cancer patients [97]. Suppression of miR-203 was correlated with lymph node metastasis (LNM) [98]. over-expression of miR-203 inhibited cervical cancer cell proliferation and angiogenesis by inhibiting BANF1 and vascular endothelial growth factor A (VEGFA) [97, 99, 100]. However, these authors identified the circulating level of miR-203 was significantly up-regulated in early stage of

cervical cancer in another study [101]. Consistently, Gocze et al. also detected miR-203 was higher in HPV positive cervical cancer group than HPV negativity group, which implicated that miR-203 played a positive role in the initiation and progression of cervical cancer [102]. Likewise, it was observed that the down-regulation of miR-203 in high risk HPV cervical cancer patients was caused by CpG-islands methylation [103]. Contradictorily, another group proved that methylation of miR-203 was not found in the cervical squamous cell carcinomas [104].

3.6. miR-203 and Ovarian Cancer

Ovarian cancer is the fifth leading cause of cancer death in women in development countries. According to the statistics, there were 14270 deaths in 2014 in United Sates [81]. miR-203 was first found to be involved in ovarian cancer development by Iorio et al. [15]. They identified an up-regulation of miR-203 level in ovarian carcinomas compared with normal tissues. Furthermore, the expression of miR-203 was significantly increased after 5-aza-2'-deoxycytidine demethylating treatment in the ovarian cell line OVCAR3, suggesting the hypomethylation of miR-203 could be the mechanism responsible for its over-expression *in vivo* [15]. Similarly, Taylor et al. also detected the hypomethylation in ovarian tumor, which resulted in the up-modulation of miR-203 [16]. Simultaneously, another study further confirmed that methylation of miR-203 was not found in ovarian cancer [104]. Strikingly, over-expression of miR-203 was indicated to be close connected with the aggressive ovarian tumor progression and poor outcome of epithelial ovarian cancer patients, suggesting miR-203 may serve as a novel molecular marker to predict the aggressive tumor progression and unfavorable prognosis of epithelial ovarian cancer patients [105]. In contrast, a recent *in vitro* study validated that miR-203 expression was down-regulated in ovarian cancer cell lines SKOV3 and OVCAR3 and functioned as tumor suppressor. miR-203 over-expression inhibited SKOV3 and OVCAR3 proliferation, migration, invasion and EMT by silencing SNAI2 [106]. The paradoxical expression of miR-203 in ovarian cancer may be caused by the sample variation in collection from different tumor stages [106].

3.7. miR-203 and Endometrial Cancer

The expression of miR-203 in endometrial cancer was inconsistent. An early study in Hong Kong women displayed an increased expression of miR-203 in endometrial adenocarcinomas compared to normal endometrium samples [107]. Conversely, miR-203 was found to be down-regulated in endometrial carcinosarcoma by Castilla et al., the low level of miR-203 led to EMT-activation and the maintenance of cell stemness [108]. Further research illustrated that hypermethylation of miR-203 was a frequent event in endometrial carcinomas, which induced loss of the SRY-related high-motility group box 4 gene (SOX4) inhibition by miR-203 [104].

4. Conclusions and Perspectives

In these years, miRNAs, which were close relevance to the pathogenesis of many cancers, have become a research hotspot. In this review, by integrating the charms of previous findings, we found miR-203 played key roles in gastrointestinal and urogenital cancers by targeting different genes which were related in cell proliferation, apoptosis, EMT, and angiogenesis. Down-regulation of miR-203 was found in HCC, stomach cancer, esophageal cancer, colorectal cancer and bladder cancer. The low level of miR-203 in these cancers seems to be led by the CpG-island methylation. And in breast cancer, down-regulation of miR-203 also contributed to methylation. Interestingly, the level of miR-203 is association with lifestyle behaviors in gastric adenocarcinoma patients. Of special note is that miR-203 is up-regulated or down-regulated in pancreatic cancer, prostate cancer, kidney cancer, breast cancer, cervical cancer, ovarian cancer and endometrial cancer. The consistent opinion to the uncertain miR-203 expression is that miR-203 tends to be up-regulated in the early stage of cancers and down-regulated in serious cancers. Specifically, it was implied that hypomethylation of miR-203 leads to its up-regulated in ovarian cancer. But the knowledge of the factors which lead to miR-203 up-regulation in these cancers is limited. Furthermore, miR-203 also could regulate the sensitivity of chemotherapy in cancers including cisplatin, but the conclusion is undetermined and further studies aimed at interrogating the regulatory mechanisms by which miR-203 in the sensitivity of cancers to chemotherapy are necessary. The distinct expression of miR-203 in different cancers indicates its tissue- or cell type-specific feature. Nevertheless, we are more likely to think that the expression of miR-203 in these cancers is a dynamic changing process. miR-203 expression is negative correlation with stage of cancers. In the early stage of cancers, the up-regulation of miR-203 acts as a tumor promoter. While in the late stage of, miR-203 methylation (except ovarian cancer) leads to its down-regulation and miR-203 plays a positive role in inhibiting tumors. When miR-203 is up-regulated in cancers, it will inhibit the sensitivity of chemotherapy, but when miR-203 is down-regulated, it will enhance the sensitivity of chemotherapy. This illustrates the complex biological functions of miR-203 and postulates that differential cancers stage may be what ultimately defines whether miR-203 functions as an oncogene or a tumor suppressor.

As highlighted in this review, the previous findings give the potentially broad function for miR-203 in the regulation of gastrointestinal and urogenital cancers. As such, there is an increasing number of studies make miR-203 an attractive prognostic marker in cancers. Nevertheless, the specific rationale to assess the role of miR-203 in these cancers remains dispute. Hopefully, we expect that as researches continued, miR-203 maybe has tremendous therapeutic potential in the treatment of cancers in the future.

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Conflicts of Interest

All the authors do not have any possible conflicts of interest.

Abbreviations

ABCE1: ATP-binding cassette sub-family E1;
ADAM: A disintegrin and metalloprotease;
AR: androgen receptor;
AREG: amphiregulin;
CASK: calcium/calmodulin-dependent serine protein kinase;
CDK: cyclin-dependent kinase;
CpG: cytosine-phosphoguanine;
CRC: colorectal cancer;
EAC: esophageal adenocarcinomas;
EGF: epidermal growth factor;
EMT: epithelial to mesenchymal transition;
EREG: epiregulin;
ESCC: esophageal squamous cell carcinoma;
EZH2: enhancer of zeste homolog 2;
HA: hyaluronan;
HCC: hepatocellular carcinoma;
HCV: hepatitis C virus;
HPV: human papillomaviruses;
IL: interleukin;
LASP: LIM and SH3 protein;
LNM: lymph node metastasis;
LT: liver transplantation;
MAPK: mitogen-activated protein kinase;
MET: mesenchymal to epithelial transition;
mRNAs: messenger RNAs;
MVD: microvessel density;
OS: overall survival;
PA: phosphatidic acid;
PanINs: pancreatic intraepithelial neoplasms;
PDAC: pancreatic ductal adenocarcinomas;
PLD: phospholipase D;
Rap1A: ras-related protein rap-1A;
RCC: renal cell carcinomas;
RFS: recurrence-free survival;
RISC: RNA induced silencing complex;
SIK: salt-inducible kinase;
SNAI2 or Slug: snail homolog 2;
Sox4: SRY-related high-motility group box 4 gene;
SOCS: suppressor of cytokine signaling;
SP: side population;
TGFA: transforming growth factor-α;
TLR: toll-like receptor;
TNF-α: tumour necrosis factor-α;
TNM: tumor nodes metastasis;
TYMS: targeting thymidylate synthase;
UTR: untranslated region;
VEGF: vascular endothelial growth factor;
ZNF: zinc finger protein

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