Role of miR-193a in cancer: a possible cancer drug target with complex factors control the pattern of its expression

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Abstract

There is emerging data suggest that miR-193a plays a key role in pathogenesis and response to chemotherapy in different types of cancers. This review aims to analyse the role of miR-193a in cancer according to the information of literature. miR-193a could acts as a tumour suppressor or oncogene in the development of cancers. Also, it could affect cancer stem cell development. In some instances, miR-193a predicts the cancer progression, invasion and metastasis as well as non-invasive method to differentiate different cancers. In addition, it modulates the response of cancer to chemotherapeutic treatment. miR-193a expression is regulated by the methylation status of its promoter region, MAX, RXR α , XB130, P63, P73, AEG-1, HOTAIR, HIFs, and EGFR proteins. To conclude, the biological significance of miR-193a in different types of cancer raises the possibility of using it as a molecular marker in predicting of cancer growth, prognosis of patients with cancer and cancer drug target.

Keywords: miR-193a; cancer; review; prognosis; mechanism; methylation

Introduction

MicroRNAs (miRNAs or miRs) play important roles in development and maintenance of many cancers. It is estimated that approximately 30% of protein coding human genome is targeted by miRNAs [1]. In addition, miRNAs can act either as an oncogene or as a tumour suppressor gene in regulating multiple cellular and pathophysiological events in carcinogenesis [2-8].

The miR-193a is a subunit of miR-193 family, which also consist of miR-193b and miR-193c, is located on chromosome 17 at 17q11.2 of human genome (Gene ID: 406968) [9]. Based on arm selection, miR-193a can be subdivided to miR-193a-3p and miR-193a-5p. Although miR-193a and miR-193b are related miRNAs that share 18 of 22 nucleotides and possess the identical 8-nucleotide seed sequence, they are encoded by different genes located on different chromosomes [10]. miR-193c differs from miR-193b by one nucleotide at position 21 and by the absence of three Us at the 3' end [11].

Inhibitory role of miR-193a has been identified in many types of cancers. miR-193a acts as a tumour suppressor gene in leukaemia [12-15], lung cancer [16-21] and breast carcinomas [22]. miR-193a aberrantly silenced by DNA hyper methylation which lead to inhibiting its protective role and enhancing cancer development [23,12,24]. In contrast, miR-193a is reported to have oncogenic effect in other types of cancers like prostatic adenocarcinoma [25] and colorectal adenocarcinomas [26]. In this review we aimed to critically review the different roles of miR-193a in various cancers and to identify the factors that regulate its expression.

The roles of miR-193a in development of the cancers

miR-193a often acts as tumour suppressor in the development of cancer (Table 1).

In leukaemia, miR-193a has been involved in the pathogenesis of leukaemia by targeting *c-kit* gene (V-Kit Hardy-Zuckerman 4 Feline Sarcoma Viral Oncogene) [12]. It is understood that the c-kit protein is over expressed in approximately 80% of the acute myeloid leukaemia cases [27]. The upregulation of miR-193a blocks the cell cycle progression in myeloid leukaemia by targeting several genes involved like *AML1* (*Acute myeloid leukaemia 1*), *ETO* (*Eight twenty one*), *KIT*, *CCDDN1* (*Cyclin D1*) and *MDM2* (*Mouse double minute 2 homolog*) [13].

The tumour suppressor role of miR-193a was noted in malignant pleural mesothelioma [28]. Transfections of malignant pleural mesothelioma cell lines with miR-193a-3p and miR-193a-5p have proliferation inhibitory effect; miR-193a-5p has less inhibitory role than miR-193a-3p [28]. This may indicate that miR-193a-3p has more tumour suppressor properties than miR-193a-5p in this type of tumour and may be in other types which need to further investigation. Also, delivery of miR-193a-3p mimic inhibits malignant pleural mesothelioma xenograft tumour growth with an increase in apoptosis which is determined by terminal deoxynucleotidyl transferase dUTP nick end labelling assay [28].

In lung carcinomas, significant downregulation of miR-193a-3p has been reported in large cohort of the patients with non-small cell lung carcinoma (NSCLC) when compared to match non-neoplastic tissue [29]. The authors reported that miR-193a-3p targets *AEG-1* (astrocyte elevated gene-1) in NSCLC [29]. Expression of AEG-1 plays important role in the carcinogenesis of NSCLC and could inhibit the apoptosis by enhancing the level of anti-apoptotic protein Bcl-2 [30]. Another study showed that overexpression of miR-193a-3P inhibits the proliferation and enhances the apoptosis in several NSCLC cell lines [19].

In breast carcinoma, tumour suppressor role of miR-193a had been proven [10, 31, 32, 33, 22]. miR-193a-3p has significant effect on several proteins controlling G1/S phase

transition of cell cycle in breast carcinoma cell lines (MDA-MB-231 and MCF) by targeting JNK1 (Jun N-terminal kinases1), a cytosolic kinase member of mitogen-activated protein kinase (MAPK) [32]. High expression of JNK1 was reported in many cancers [34]. Furthermore, miR-193a-3p co-operates with miR-9-5p to target multiple genes involved in oestrogen receptor (ER) signalling pathway in breast cancers [22]. miR-193a-5p also reported to have important role in the regulation HER2 (human epidermal growth factor 2) in breast cancer [35]. Tahiri and his colleagues showed that miR-193a-3p has downregulated in both tissues samples from breast carcinomas and core needle biopsies from benign tumours of fibroadenomas and fibroadenomatosis [33]. By doing miRNA microarrays followed by Quantitative Real-Time PCR; Tahiri *et al* showed that this miRNA similarly deregulated in both benign and malignant tumours of the breast. Also, restoration the level of miR-193a-3p by transfection the breast cancer cell lines confirmed the growth inhibitory properties of this miRNA [33].

Studies using both *in vivo* and *in vitro* analysis have showed that miR-193a has a significant role in the development of hepatocellular carcinoma. Salvi *et al* found that the transfection of hepatocellular carcinoma cell lines (HA22T/VGH) with pre-miR-193a resulted in inhibiting the tumour growth by targeting *UPA* (Urokinase, Plasminogen Activator) [36]. It is noteworthy that high UPA level plays important roles in tumour progression and metastasis. By using qRT-PCR, significant downregulation of miR-193a-3p was noted in 95 hepatocellular carcinoma tissues when compared with their corresponding non-neoplastic tissue of the same patient [37].

Iliopoulos *et al* showed that miR-193a functions as a tumour suppressor gene in HCT-29 and HCT-116 colon cancer cell lines (HCT-29 and HCT-116) [10]. Also, miR-193a-3p showed inhibitory role in a glioblastoma cell line (U-87) by targeting *JNK1* and *MCL-1* genes as well as in glioblastomas U-251 cell line by targeting *MCL-1* [32, 38].

In female genital tract, miR-193a-3p was reported to induce apoptotic cell death in A2780 cell line of ovarian cancer by targeting an apoptotic protein from BCL2 family gene, myeloid leukaemia cell differentiation protein-1 (Mcl-1) [39]. Also, down regulation of miR-193a-5p increases the expression of *YY1* oncogene (Yin Yang 1), and epigenetically silences the APC (adenomatous polyposis coli) gene in endometrial adenocarcinoma [40]. Decrease of APC results in activation of downstream target genes which are increasing the cell proliferation and migration and that are contributing to the endometrial adenocarcinoma development [40]. The authors confirm the miR-193a-5P downregulation in tissue samples of 122 primary endometrial adenocarcinoma and injection of miR-193a-5p oligos in to endometrial adenocarcinoma xenograft tumour significantly inhibits the cancer growth by downregulation of *YY1* gene expression [40].

miR-193a also has oncogenic properties in cancers (Table 2). miR-193a-3p was significantly upregulated in both tissues and blood samples of patients with colorectal adenocarcinoma [26]. The authors did miRNAs microarray in 30 tissues (matched cancer and non-cancerous tissues) and blood samples from 42 patients. Then, validation of these results by RT-PCR in another sets of both tissue and blood samples were done [26].

miR-193a-3p was noted to be one of the most upregulated miRNAs in response to hypoxia in U-87 malignant glioma cell line and in tissue samples of 30 patients [41]. The authors demonstrate these finding by using next generation sequencing, miRNA microarray and quantitative RT-PCR [41]. The results also showed that the expression of miR-193a-3p is HIF-1(Hypoxia-inducible factor 1) dependent [41].

By using RT2 PCR arrays, miR-193a-5P also showed a significant upregulation in prostate adenocarcinoma tissues compared to non-neoplastic tissue [25].

Role of miR-193a in cancer stem cells

Stem cells play vital roles in tumour initiation, progression, metastasis and chemoresistances in cancers. Long term suppression of miR-193a can trigger the formation of ovarian cancer initiating cell by targeting a stem cell factor receptor, *c-KIT* [42]. Additionally, miR-193a has shown to be downregulated in a breast cancer cell line (MCF-10) which contains ER (oestrogen receptor)-Src (non-receptor tyrosine kinase) fusion protein after treatment with tamoxifen that block the oestrogen receptor [10]. Studies have proved that treatment with tamoxifen can lead to formation of mammospheres enriched with breast cancer stem cells [10]. Downregulation of miR-193a in these cells have resulted in increased tumorigenicity and invasiveness by targeting *K-RAS* (Kirsten Rat Sarcoma Viral Oncogene Homolog) and *PLAU* respectively [10]. Upregulation of miR-193a has also been reported in colon cancer stem cells (CSCs) in other studies. By using miRNAs microarray, Yu *et al.* reported miR-193a-3p overexpression in cancer stem cells compared to non-cancer stem cells from SW116 colon cell lines [43]. Another study by Xu *et al* has determined that miR-193a-3p amongst the up regulated miRNAs which are differentially expressed between side population and non-side population cells of colon cancers [44]. Thus, deregulation of miR-193a in different types of cancer stem cells is obvious. Altered expression levels and its association with cancer stem cells raise the complexity in the biological behaviour of miR-193a which need to further investigations.

The role of miR-193a in cancer progression, invasion and metastasis

miR-193a was reported to have important roles in cancer progression, invasiveness and metastasis. Invasiveness and distant metastasis in cancers cause one of the biggest challenges in cancer therapy. Previous studies have observed that miR-193a repress the invasion and metastasis in some cancers. For examples, miR-193a-3p reduces the metastasis

and invasion of human NSCLC by targeting *ERBB* signalling pathway [17, 18]. *ERBB* is a family of oncogenes composed of four receptors tyrosine kinases that are deregulated in different types of cancers including lung cancer [45]. Transfection of highly metastatic NSCLC with miR-193a-3p mimic resulted in suppressing the migration of the cells, reversing the epithelial-mesenchymal transition and reducing the metastatic nodules formation in nude injected mice [18]. In addition, proteomic analysis assists in identifying specific proteins which are directly affected by the miR-193a expression in metastatic cancer. For example, Deng and his colleagues identified that GSN (Gelsolin) and PPP2R2A (protein phosphatase 2, regulatory subunit B, alpha) were upregulated in cancer cell line from metastatic non-small cell lung cancer (SPC-A-1sci) and they implicated in miR-193a-3p directed inhibition of metastatic NSCLC [16]. Furthermore, that the low expression of miR-193a-3p was significantly associated with lymph node metastasis and NSCLCs with advanced pathological stages (stage III and IV) [29].

A similar trend of clinical correlation was noted in colorectal carcinoma. Downregulation of miR-193a-5p had significant correlation with lymph node metastasis and venous invasion in patients with colorectal cancer [46]. Thirty-seven of 55 patients with lymph node metastases showed low expression of miR-193a-5p and there were 13 of 16 patients with venous invasion expressed low level of miR-193a-5p in the colorectal cancer tissues [46]. Also miR-193a down regulation was associated with poor survival of the patients with acute myeloid leukaemia [13]. The above studies give evidences support that miR-193a downregulation have been implicated in invasion and metastasis of different types of cancers.

On the other hand, significant up-regulation of miR-193a-3p was reported in other studies and has been contributed to the roles of this miRNA in invasion and metastasis. For examples, significant upregulation of miR-193a-3p was noted in metastatic medullary thyroid

carcinoma tissues [47]. The authors confirmed significant upregulation of miR-193a-3p in tissue samples with metastatic medullary carcinoma when compared to primary medullary carcinoma by using qRT-PCR and in situ hybridization [47]. Moreover, significant upregulation of miR-193a-5p was also reported in high grade prostatic adenocarcinomas (Gleason score ≥ 8) tissue samples [25]. Also, the expression level of miR-193a-3p increased significantly in blood samples of colorectal cancer patients with advanced stages [26]. By using the Illumina HiSeq platform-miRNA microarray analysis, miR-193a appears to be significantly upregulated in muscle invasive urothelial carcinoma of bladder and subsequent data analysis reveals its correlation significantly with pathologic T, N stages, and histologic grades [48]. High expression of miR-193a was associated with poorer survival of the patients with muscle-invasive urothelial carcinoma of bladder [48].

The role of miR-193a in differentiating the different cancers

It is difficult sometime to differentiate between some types of cancers without using invasive measures. Benjamin *et al.* identified that miR-193a-3p and miR-192 can be used to differentiate malignant pleural mesothelioma from lung adenocarcinoma with specificity of 94% and sensitivity of 100% [49]. The authors developed an assay composed from three phases (Discovery Phase, Training Phase and validation phase) to compare miRNAs expression between malignant pleural mesothelioma and lung adenocarcinoma [49]. The diagnosis based on miRNAs assay is in agreement of histological diagnosis in most of the cases. In addition, it was found that miR-193a had a lowest expression in acute myeloid leukaemia-M2 subtype comparing to other subtypes of acute myeloid leukaemia [13]. Acute myeloid leukaemia subtype-M2 is characterized by a translocation of a part of chromosome 8 to chromosome 21 (a chromosomal change which is associated with more successful treatment). Other studies on brain tumours have reported that Wnt type medulloblastoma

showed significant upregulation of miR-193a-3p compared to other subgroups of medulloblastoma [50, 51]. Taken together, this information may raise the possibility of using miR-193a in differentiating some types of cancers.

The role of miR-193a in modulating the chemotherapeutic treatment

New evidences suggesting the role of miR-193a in modulating the sensitivity of several chemotherapeutic treatments raise the possibility of targeting miR-193a in future cancer therapies. In 2014, Lv *et al* found that the high expression of miR-193a-3P increases the chemo resistance of urothelial carcinoma of bladder to several chemotherapeutic treatments such as pirarubicin, epirubicin hydrochloride and adriamycin by targeting *SRSF2* (Serine/Arginine-Rich Splicing Factor 2), *PLAU* and *HIC2* (Hyper methylated In Cancer 2) [52]. Both *SRSF2* and *PLAU* were reported previously as direct targets for miR-193a in other types of cancers [53, 10]. Several pathways were involved in this process including DNA damage, NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells), Myc/Max (Avian Myelocytomatosis Viral oncogene Homolog /myc-associated factor X), oxidative stress and Notch signalling pathways [52]. In addition, Deng *et al.* found that miR-193a-3p expression was over 100-fold change higher in H-bc cells (the multi chemo resistant bladder cancer cell line) than in 5637 cells (the multi chemo sensitive bladder cancer cell line) [54]. Moreover, overexpression of miR-193a-3p in 5637 cells led to reduction in cell death triggered by four chemotherapeutic drugs (pirarubicin, epirubicin hydrochloride, paclitaxel and cisplatin) via repressing a tumour suppressor gene, *LOXL4* (*Lysyl Oxidase-Like 4*), and by targeting the oxidative stress pathway [54].

miR-193a-3p also enhances the chemo resistance in urothelial carcinoma of bladder by targeting other regulatory genes. Many recent studies have showed that miR-193a-3p can modulate the resistance of the urinary bladder carcinoma to chemotherapeutic drugs by

modulating various downstream targets such as *PSEN1* (Presenilin 1), *ING5* (*Inhibitor Of Growth Family, Member 5*) and *HOXC 9* (Homeobox C9) [55-57]. *ING5* is well known for its tumour suppressor role and *PSEN1* is known for its association with Alzheimer's disease and in the cleavage of the Notch receptor. *HOXC9* belongs to the family of transcriptional factors that play critical roles in cell differentiation. Similar to urinary bladder cancers, miR-193a has also been noted for chemo resistance in liver, ovarian and oesophageal carcinomas [53,58, 59]. miR193a-3p was found to be upregulated in a hepatocellular carcinoma cell line resistant to 5- fluorouracil (SMMC-7721). Repression of miR-193a-3p in these cells decreases the size of cancer and sensitizes the cells to 5 fluorouracil treatments [53]. Another study on ovarian carcinoma revealed that the expression of miR-193a-5p was increased in patients with ovarian carcinoma who are refractory to non-adjuvant chemotherapy [58]. Similar to these findings, miR-193a-3P enhances the chemo resistant of oesophageal carcinoma cells by targeting *PSEN1* [59].

In contrast to these findings, miR-193a was reported to sensitize tumour cells to chemotherapeutic treatment in other types of cancers. For example, overexpression of miR-193a-3p significantly downregulated its target gene *NCOA3* (Nuclear Receptor Coactivator 3) and sensitized the oestrogen receptor positive breast cancer cells to tamoxifen treatment [22]. It is noteworthy that *NCOA3* was overexpressed up to 60% in breast cancer [60]. In colon cancer cells, miR-193a overexpression has led to sensitise the cancer cells (HCT116) to BCL2 inhibitor, ABT-263 (Navitoclax), by 50% [61]. These studies suggest that miR-193a plays an important role in modulating the cancer cell response to several chemotherapeutic treatments by targeting different genes

Factors regulating miR-193a expression in cancers

Several factors were reported to have effects on the expression pattern of miR-193a in different types of cancer. Some of these factors were reported based on several studies and others based on single studies, these factors include:

DNA methylation state of miR-193

Tumour suppressor or oncogenic roles and other functional significance of miR-193a have been reported to be associated with the methylation state of its promoter region. Methylation state of miR-193a promoter region is one of the most important factors which have studied by several groups.

Gao *et al* in 2011 has first reported hyper methylation of miR-193a in acute myeloid leukaemia [12], followed by Heller *et al* reporting the feature in non-small cell lung carcinomas [20]. In contrast, this microRNA was found to be hypo methylated in other types of cancers. For example, miR-193a-3P is significantly hypo methylated in SMMC-7721 (hepatocellular carcinoma cell line resistant to 5- fluorouracil), that explain why this miRNA can act as oncogene in such type of cancer by targeting *SRSF2* [53]. *SRSF2* encode the Serine/arginine-rich splicing factor 2 protein that plays important roles in splicing of mRNA precursors, mutation of this gene is frequently reported in patients with myelodysplastic syndrome and some types of leukaemia [62]. miR-193a-3P is also noted to be hypo methylated in multi-chemo resistance urinary bladder cancer cell lines (H.bc). Injection of antagomiR-193a-3P in to urinary bladder cancer cells in mice leads to decrease the cancer size indicating its behaviour as a tumour oncogene due to hypo methylation of its promoter region [52].

The methylation state of this gene was differentially expressed amongst different types of cell lines in the same type of cancer and has affected the expression pattern of this

miRNA in these cell lines. miR-193a is hyper methylated in 5637 (multi-chemo sensitive bladder cancer cell line), the average CPG methylation is 78.6% while it is hypo methylated in H-bc, the average CPG methylation is 4.3% [52]. Moreover, the miR-193a gene was at the top of the most differentially methylated CPG in hepatocellular carcinoma. It was hypo methylated in hepatocellular carcinoma cell line resistant to 5- fluorouracil (SMMC-7721) whereas hyper methylated in QGY-7703 (hepatocellular carcinoma cell line sensitive to 5- fluorouracil) [53].

The methylation state of miR-193a was also reported to have no effect on the miR-193a expression in some cancers. For example, miR-193a was expressed even in cell lines with complete methylation in gastric cancer [63]. Furthermore, measuring the expression level of miR-193a-3p in 10 types of malignant pleural mesothelioma after treatment with 5-aza-2'-deoxycytidine (DNA methylation inhibitor) showed that there is only 3-fold increase in miR-193a-3P expression in H28 cell line; the other 9 cell lines showed slightly decrease in miR-193a-3P [28]. Moreover, methylation of miR-193a-3p promoter region was not detected in all except one malignant pleural mesothelioma cell line without making significant difference in its expression level [28]. Several studies proved the effect of the methylation state on miR-193a expression. However, other studies proved that the miR-193a methylation state is not common event in some types of cancer. Even if it presents, it does not affect the expression pattern of miR-193a. The methylation state and its effect on the expression pattern of miR-193a may be cancer specific event.

Long non- coding RNAs (lncRNAs)

Long non- coding RNAs (lncRNAs) may play a role in regulating the expression of miR-193a in cancer. HOTAIR (Homeobox (HOX) transcript antisense RNA) has a significant role in cancer invasiveness and metastasis [64- 67]. Recently, HOTAIR identified

as one of competing endogenous RNAs (ceRNAs) that acts as a natural sponge to bind miR-193a and inhibit its function in acute myeloid leukaemia [15]. Similar to this finding, urothelial carcinoma-associated 1 (UCA1) which is another type of long non-coding RNAs, identified as a molecular sponge to miR-193a-3P in non-small cell lung carcinoma [68]. UCA1 revokes the tumour suppressor effect of miR-193a-3P on its target *ERBB4* in non-small cell lung carcinoma [68]. The future may give other evidences about the role of such types of RNAs in regulating miR-193a and other types of miRNAs.

Max and RXR α

Max (MYC associated factor X) is a type of phosphoprotein composed of two main isoforms (P21 and P22). Both isoforms have unique transcription and biological activities but they have different DNA binding [69]. RXR α (Retinoid X receptor alpha) is a member of retinoid X receptors (RXRs) which are ligands dependent transcriptional factors that play critical role in cell growth and differentiation by interacting with different cancer molecular pathways [70]. Both Max and RXR α bind directly to the promoter region of miR-193a and regulate this miRNA during the process of transformation of breast cancer cell line (MCF-10) treated with tamoxifen [10]. Chromatin immunoprecipitation showed that Max and RXR α bind to the miR-193a regulatory region in oestrogen receptor-Src (non-receptor tyrosine kinase) breast cancer transformed cells [10]. Moreover, Max and to a lesser extent RXR α repress the miR-193a transcription significantly at later stages of cellular transformation [10]. Thus, a combination of both Max and RXR α are involving in the process of miR-193a transcription.

XB 130

XB130 (also known as actin filament associated protein 1-like2, AFAPIL2) is a member of adaptor proteins which are involved in intracellular signal transductions and cellular motility [71]. XB130 has been reported as a potent regulator of several miRNAs including miR-193a-3p [72]. Based on their study, Takeshita and his colleagues validated the upregulation miR-193a-3p in XB130 knockdown thyroid cancer cells [72]. In addition, overexpression of miR-193a-3p significantly induced both early and late apoptosis in XB130 knockdown thyroid cancer cells [72]. Furthermore, the expression of pri-miR-193a-3P was also increased in XB130 knockdown cells [72]. Quantitative real time PCR was used to quantify the amount of mature and pri-miR-193a-3p in these cells suggesting that the transcription of pri-miRNAs may also controlled by XB130.

P63 and P73

P63 and P73 are P53 transcription factors family members that play an integral role in DNA damage response and tumorigenesis [73]. These two transcription factors are validated as miR-193a direct regulators [74]. The P73 function as a direct transcriptional activator of miR-193a whereas P63 function as a transcriptional repressor for this miRNA in head and neck squamous cell carcinoma [74]. Knockdown of P73 resulted in down regulation of miR-193a while knockdown of P63 lead to up regulation of miR-193a. These results were confirmed later by luciferase assays [74]. In addition, there is UTR-dependent regulation of multiple P73 isoforms by feedback loop from miR-193a [75]. The results of these studies demonstrated the complex roles for miR-193a in this type of the cancers which is mediated by both P63 and P73 transcription factors.

Impaired Drosha, DGCR8 and Dicer function

Drosha is RNase III enzyme binds to the protein DGCR8 which is in humans is encoded by *DGCR8* gene (*DiGeorge Syndrome critical region gene 8*) to form microprocessor complex that cleaves the pri-miRNAs to pre-miRNAs. Dicer is enzyme belong to RNase III family that cleaves the pre-miRNAs to mature-miRNAs.

Downregulation of miR-193a can be attributed to other cause rather than reduced gene transcription. Some studies showed that poor function of Drosha and Dicer is associated with certain subgroups of breast cancer [76]. Another study has noted reduced levels of Drosha/DGCR 8 and low level of mature miR-193a in high UPA-expressing cells of breast cancer [31]. Moreover, an increased level of miR-193a expression was noted in these cells followed by forced expression of Drosha/DGCR8 [31]. These findings suggest that the downregulation of this miRNA in invasive breast cancer might be attributed to inefficient processing of miR-193a by Drosha/DGCR8.

Astrocyte elevated gene-1 (AEG-1)

AEG-1 plays important role in angiogenesis, invasion, metastasis and chemo resistance [77]. *AEG-1* has been also reported to have role in regulating RNA-induced silencing complexes (RISC) and miRNA expressions in cancer [78]. Huang *et al.* identified that the AEG-1 can modify the expression pattern of miR-193a in colon cancer cell lines [79]. Downregulation of miR-193a has been noted in colon cancer cell line which showed at the same time upregulation of AEG-1 [79]. This study noted that inhibition of AEG-1 expression significantly increases the miR-193a expression and sensitize the cells to 5-fluorouracil [79].

HIFs (Hypoxia-inducible factors)

HIFs are transcription factors mediate the effect of hypoxia in cellular environment [80]. miR-193a-3p showed a significant increase in HIF1A transfected glioblastoma cell line (U87MG) which represent stage IV brain cancer. Downregulation of HIF1A resulted in downregulation of miR-193a-3P in these cells [41]. That means this factor acts synergistically to increase the miR-193a expression. However, the expression of miR-193a-3P did not show significant change in response to HIF1 A transfection in other glioblastoma cell line (U 251 MG) which represent human glioblastoma astrocytoma grade III [41]. These results may suggest the difference in the regulatory process of this miRNA in different cell lines which may be attributed to the difference in cells genotypes.

EGFR

EGFR (Epidermal Growth Factor Receptor) is a member of the ErbB family receptors, a subfamily of four closely related receptor tyrosine kinases: EGFR (ErbB-1), HER2/c-neu (ErbB-2), Her 3 (ErbB-3) and Her 4 (ErbB-4). EGFR suppresses the maturation of some tumour-suppressor miRNAs including miR-193a [81]. Under hypoxia, EGFR phosphorylate the argonaute 2 (AGO2) at Tyr 393, this process in turn reduces the binding of Dicer to AGO2 [81]. Reduction in Dicer-AGO2 interaction resulted in less loading of the miR-193a-5p precursor consequently leads to decrease loading of mature miR-193a-5p on to RISC (RNA-induced silencing complex) [81]. This finding can explain one factor behind the downregulation of miR-193a in some types of cancers.

Conclusion

It is clear that miR-193a has complex biological behaviour as their expression pattern is different in many cancers. Also, miR193a affects different process in the pathogenesis, development and chemoresistance in cancer. Thus, miR-193a has potential to be used as a molecular target alone or in-conjunction with other targets in predicting the progression and prognosis of various cancers.

Conflict of Interest: None

Acknowledgement: None

Table 1: Studies which report miR-193a as a tumour suppressor gene

Author/ year	miR	type of Cancer	type of study	Cell Lines	Type of in vivo	Target genes
Wang/ 2013	193a-3P	NSCL	<i>in vitro</i>	NCI-H 1993/ NCI-H 1915/ A427/ NCI-H 2073		
Liang/ 2015	193a-3P	NSCL	<i>in vitro</i> <i>in vivo</i>	A549, HCC 827, H1975	human tissue, mouse	<i>ERBB4</i>
Yu/ 2015	193a-3P	NSCL	<i>in vitro</i> <i>in vivo</i>	SPC- A-1SCI SPC-A-1	human tissue	<i>ERBB4</i> , <i>S6K2</i>
Ren/ 2015	193a-3P	NSCL	<i>in vivo</i>		human tissues	<i>AEG-1</i>
Williams /2015	193a-3P 193a-5P	Malignant mesothelioma	<i>in vivo</i> <i>in vitro</i>	MSTO -H211	human tissues	<i>MCL-1</i>
Iliopoulos /2011	193a	Colorectal carcinoma	<i>in vivo</i> <i>in vitro</i>	HCT- 116 HT- 29	human tissue mouse	<i>KRAS</i> <i>PLAU</i>
Zhang/ 2014	193a-5P	Colorectal carcinoma	<i>in vivo</i>		human tissue	
Lam 2010	193a	Colorectal carcinoma	<i>in vitro</i>	HCT- 116		
Uhlmann /2012	193a-3P	Glioblastoma	<i>in vitro</i>	U-87		<i>JNK1</i>
Kwon /2013	193a-3P	Glioblastoma	<i>in vitro</i>	U-251		<i>MCL-1</i>
Gokhale /2010	193a-3P	Medullo- blastoma	<i>in vitro</i> <i>in vivo</i>	Doay	human tissue	
Salvi/ 2013	193a-3P	HCC	<i>in vivo</i> <i>in vitro</i>	HA22J /VGH	human tissue	<i>UPA</i>

Liu/ 2015	193a-3P	HCC	<i>in vivo</i>		human tissue	
He/ 2013	193a-5P	Prostate carcinoma	<i>in vivo</i>		human tissue	
Kwon/ 2013	193a-3P	Cervical carcinoma	<i>in vitro</i>	Hela		<i>MCL-1</i>
Nakano/ 2013	193a-3P	Ovarian carcinoma	<i>in vitro</i>	A2780		<i>MCL</i>
Yang/ 2013	193a-5P	Endometrial carcinoma	<i>in vivo</i>		human tissue	<i>YYI</i>
Iliopoulos/ 2011	193a	Breast carcinoma	<i>in vitro</i>	MDA- MB- 231		<i>KRAS</i> <i>UPA</i>
Noh/ 2011	193a	Breast carcinoma	<i>in vitro</i>	MDA- MB- 231		<i>PLAU</i>
				MDA- MB- 436		
Pillai/ 2014	193a-3P	Breast carcinoma	<i>in vitro</i>	MCF7		<i>NCOA3</i>
Gao/ 2011	193a	AML	<i>in vivo</i> <i>in vitro</i>	kasumi human -1 BM K562		<i>c-Kit</i>
Li/ 2013	193a	AML	<i>in vitro</i> <i>In vitro</i>	SKNO-1 Kasumi-1		<i>ETO</i>

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BM: Bone Marrow; NSCL: Non-small cell lung carcinoma; HCC: hepatocellular carcinoma;
AML: Acute myeloid leukaemia

Table 2: Studies which report miR-193a as a tumour oncogene and/or to have a role in chemo resistance

Author/miR Year	type of Cancer	type of study	Cell Lines	Type of in vivo	Target genes
Deng/ 2014	193a-3P Urothelial carcinoma	<i>in vitro</i> <i>in vivo</i>	H-bc	mice	<i>LOXL4</i>
Lv/ 2014	193a-3P Urothelial carcinoma	<i>in vitro</i> <i>in vivo</i>	H-bc	mice	<i>SRSE2</i> , <i>PLAU</i> <i>HIC2</i>
Deng/ 2015	193a-3P Urothelial carcinoma	<i>in vitro</i> <i>in vivo</i>	H-bc	mice	<i>PSEN</i>
Li/ 2015	193a-3P Urothelial carcinoma	<i>in vitro</i> <i>in vivo</i>	H-bc	mice	<i>ING5</i>
Lu/ 2015	193a-3P Urothelial carcinoma	<i>in vitro</i> <i>in vivo</i>	H-bc	mice	<i>HOXC9</i>
Xu/ 2015	193a Urothelial carcinoma	<i>in vivo</i>	-	human tissue	
Yong/ 2013	193a-3P Colorectal adenocarcinoma	<i>in vivo</i>	-	human tissue blood samples	-
Ma/ 2012	193a-3P Hepatocellar carcinoma	<i>in vitro</i> <i>in vivo</i>	SMM C-7721	mice	-
Walter /2013	193a-5P Prostate adenocarcinoma	<i>in vivo</i>	-	human tissue	-
Mariani /2015	193a-5P Ovarian adenocarcinoma	<i>in vivo</i> <i>in vitro</i>	SKOV3 OV2774	human tissue	-
Santarpia /2013	193a-3P Thyroid medullary carcinoma	<i>in vivo</i>	-	human tissue	-

Figure Legends

Figure 1: **The factors that affect and regulate the expression pattern of miR-193a in cancers.** Down regulation and up regulation of miR-193a are under the control of several factors. Some of these factors like DGCR8, Drosha and XB130 act on the pri-miR-193a. Dicer and EGFR act on pre-miR-193a. The other factors including hypermethylation and hypomethylation of P63, Max, RXR α , AEG-1, HOTAIR, UCA1, p73, HIFs acts on mature miR-193a.

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