miR-218 as a Multifunctional Regulator of Oncogenic Processes in Different Solid Tumors

Review Article

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Abstract

microRNAs are highly conserved small non-coding regulatory RNAs that involve in post transcriptional regulating of gene expression during different cellular mechanisms. Aberration of miR-218 expression during tumorigenesis of different solid tumors has been reported by numerous studies. In current systematic review article, by using the terms "miR-218" and "cancer" we first searched for English language articles in the PubMed database, published from 1993 to April 2014. Then by a comprehensive review of related articles, we provided some new insights that highlight novel features and functions of miR-218 in initiation and progression of solid tumors. The majority of these studies propose a tumor suppressing role for miR-218 considering the fact that it is significantly down-regulated in tumor tissues compared with normal specimens. Despite accumulating body of evidence regarding tumor suppressor functions of miR-218 in solid tumors; more intensive reviewing about available miR-218 recent original studies and interpretation of existing data, revealed the multifunctional role of miR-218 in these kinds of malignancies by targeting different corresponding target genes. Take all together, MiR-218 targets different cellular processes in cancer cells and its expression pattern is in an important association with various states and features of tumors. It seems that miR-218 can increase the speed of cell cycle and cell division in lower sample grades and along with progression of cancer cells it's function changes to stabilization the cancer cells and not allowing them to invade. thats why it often shows up-regulation in lower grades and down-regulation in metastatic phase. Therefore, it seems of great importance to check samples stage, grade, lymph node metastasis status and other tumor features before evaluation of miR-218 as a prognostic or diagnostic biomarker.

Key words: Biomarkers; Cancer; microRNA

Over the last decade progress has been made leading to the discovery of hundreds of small non-coding RNAs (ncRNA). A fraction of these non-coding transcripts was denoted as microRNAs (miRNAs) due to their ~ 22-nucleotide size. miRNAs expression was demonstrated to be tightly regulated during development. This class of ncRNAs is highly conserved in both plants and animals. The most original miRNAs to be discovered, lin-4 and lin-7 in Caenorhabditiselegans (c.elegans), were found to have critical roles in controlling development timing, by regulating mRNA translation. High level of lin-4 up-regulation takes place during the transition from the first to the second larval stage (L2), whereas it occurs for lin-7 from the forth-larval (L4) stage to the adult (1,2).

miRNAs regulate hundreds to thousands of protein coding genes by post-transcriptional gene silencing in animals and plants (3). These non-coding RNAs principally target the 3'-untranslated region (UTR) of genes. However, other reports have also shown that miRNAs can also target the 5'- untranslated region and coding region of their target-mRNA (3). The fine-tuning of proteins expression via miRNAs

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can change the yield of proteins in eukaryotic cells, thus influencing the whole networks and pathways. Computational studies have revealed that miRNAs control their target-genes expression through seed region, ~8 nt at the 5' end, which is crucial for miRNA functioning (4).

Several studies in model organisms have shown that miRNAs are involved in regulating development timing, proliferation, morphogenesis, and apoptosis (5). Given the importance of this class of ncRNAs, some lines of evidence have directly linked their aberrant expression and function to the development of several pathological conditions (6-8) and carcinogenesis (9). These studies indicated that miRNAs could function as classical tumor suppressors and/or oncogenes (10-12). MiR-218 has all the earmarks of being a vertebrate particular microRNA and has now been affirmed in an extensive variety of vertebrate species. According to Lorenzo F Sempere et al. report miR-218 first found to reduce Lin-218 expression level in mouse P19 cell lines through neural differentiation. Additionally they identified conserved predicted binding sites in mammalian lin-8 3-UTR messenger RNAs (13). MiR-218 could provide invaluable. information to analysis of human disease and it is nearly connected with different malignancies. Associations between miR-218 expression and clinicopathological feature of different cancer samples reported by numerous studies (14-16). Circulating miR-218 represents potential biomarker for early diagnosis and prognosis of kidney cancer, esophageal squamous cell carcinoma, esophageal cancer, glioma and hepatocellular carcinoma (17-21).

Previously performed expression signature studies demonstrated that miR-218 is under-expressed in various types of human cancers, including esophageal, cervical, lung squamous cell carcinomas, hypopharyngeal, maxillary sinus, in addition to bladder cancer and renal cell carcinomas. Recent functional studies indicated that miR-218 acts as a tumor-suppressor miRNA through inhibiting cancer cells proliferation and invasion, via targeting oncogenic genes (14, 22-25). On the other hand, other studies confirmed that miR-218 is up-regulated in pancreatic cancer (26) resulting in controversial attitude toward precise molecular role of miR-218 in different types of cancer.

In current review, first we have provided a brief summary of miRNA biogenesis and mechanisms of their deregulation during malignances. Then, by providing a comprehensive literature mining of the studies representing oncogenic or tumor suppressor role of miR-218, we seek to delineate the precise molecular function of miR-218 in various types of cancer and resolve controversial ideas about it. We will also discuss overall opinions about the possibility of employing miR-218 as a diagnostic/prognostic biomarker. We preferentially selected articles with mechanistic data supporting expressional findings on the role of miRNA-218 in several human cancers namely cervical, breast, brain, pancreatic, gastric, liver, prostate and lung squamous cell cancer.

Method:

Literature search

On February 1, 2015, we search Pubmed repository for a detailed literature linking between miR-218 and human cancers. The following key words were utilized: miR-218 OR miRNA-218 OR microRNA-218 AND cancer OR tumor OR malignancy AND cervical OR breast OR lung squamous cell cancer OR brain OR pancreatic OR gastric OR liver OR prostate.

Literature selection

English-written reports, with sufficient scientific details, as well as with extraordinary novelty were selected. We preferentially selected articles with mechanistic data supporting expressional findings. We mined full reports and searched their references for relevant missing manuscripts.

Literature Synthesis

Our literature search retrieved 160 manuscripts. We selected 124 that were of sufficient reporting rigor or novelty. We mainly employed articles that revealed mechanistic data about miR-218 function in different human cancers. Additionally, we excluded non-human studies as well as polymorphism reports.

Introduction To MiR-218

MiRNA biogenesis and function

The maturation of 20-23 nt miRNA molecules involves a multi-step excision process of the primary miRNAtranscript (pri-miRNAs) containing one or more 70 nt hairpin miRNA precursors (pre-miRNA). Pri-miRNA itself may vary in size from 100 bp to more than 10 kb, and they may have their own promoters or share promoters with other coding genes. The Primary transcripts might also contain polycistronically-arranged miRNAs, introns and

exons of protein coding genes (27). In the nucleus, these hairpin structures are recognized by a double stranded RNA-binding protein called DGCR8 as well as by an RNAselll molecule known as Drosha, and excised to produce pre-miRNAs. Subsequently, pre-miRNAs are transported via exportin 5 (XPO5) to the cytoplasm, to be processed furthermore by Dicer complex, containing DICER1, dsRPBs (TRBP and/or PRKRA), to yield an RNA intermediate duplex, comprising the mature miRNA and miRNA* sequences. While miRNA sequence is loaded into miRNA-containing ribonucleoprotein complex (RBPs), known as miRNA-induced silencing complex (miRISC), miRNA* is released and degraded. miRISC contains a member of Argonate/EIF2C protein family (Ago2) that is responsible formiRNA binding and target mRNA recognition. Moreover, other RBPs are associated with miRNA biogenesis, including DHX9, DDX6, MOV10, DDX5, DDX17, LIN28A, HNRNPA1 and KSRP (28). MiRNAs can be modified subsequently following their transcription by several enzymes; they can be edited by deaminases, or pre-miRNAs may be uridylated by uridyltransferases. These modifications may affect the sequences of miRNA and miRNA*, or their amount and ratio (29,30).

Several reports have indicated that a subset of miRNAs bypass the universal miRNA maturation order and their trimming can be independent of DGCR8 and Drosha, or are DICER1-independent (31-33), such as miR-320/miR-484 and miR-451 respectively.

Micro-RNAs do not act as naked RNAs;instead, they function as effector complexes, through recruiting members of miRIS Capparatus.The mature miRNA molecule incorporated within the complex, determines the fate of mRNA-target molecule. As mentioned previously, miRNA binds through its 6mer to 8mer seed sequence to the 3'UTR of the mRNA molecule. The nature of miRNA-target mRNA complementarity determines the fate of the mRNA; complete complementarity drives the mRNA to degradation, whereas incomplete matching prevents the translation of mRNA (28).

MiRNAs deregulation in cancer

miRNAs comprise 1-2% of all genes in different organisms; including mammals (3), and it is predicted that every miRNA regulates hundreds of target genes, making regulating protein coding genes their major objective (34). Hence, every biological process is subjected to miRNA dependent regulation. Mostly the physiological functions of miRNAs were deduced through overexpression studies in both model organisms and cell lines, and through antisense-molecules mediated knock down of the target miRNAs. These experiments have assigned crucial regulatory roles to miRNAs in processes such as cell proliferation, differentiation and survival, and have attributed them as vital players during normal development, homeostasis, and disease (11,35-38).

The aberrant miRNA expression may happen as consequence of genetic loss or gain (39), epigenetic silencing (40,41), genetic mutations (42) altering miRNAs' seed sequence, and widespread of transcriptional repressions (28). Additionally, defects in the key components of miRNA processing machinery, such as Drosha, DGCR8, DICER1, TRBP and XPO5, were also documented to be involved in promoting tumorigenesis (43-47). Moreover, miRNAs down regulation have been found to be associated with various malignancies, suggesting that these miRNAs might be tumor suppressors as their exogenous over expression suppresseson cogenesis (48). On the other hand, a significant number of studies and clinical experiments propose that a subset miRNAs may function as oncogenes, annotated as "oncomirs". These miRNAs promote tumorigenesis through inhibiting tumor suppressor genes (49) and/or genes that control cellular differentiation/apoptosis (50). These ncRNAs are significantly overexpressed in various different cancers (10).

Evidences from clinical studies, suggest that miRNAs play significant roles in the initiation, development and metastasis of many human cancers (51). Subsequently, deregulated miRNAs with expression profiles correlating with the stages of cancer, could play potential role as diagnostic and prognostic biomarkers of cancer (52,53), and the identification of aberrantly expressed miRNA is an important milestone towards elucidating miRNA-mediated oncogenic pathways.

MiR-218: genomic structure and functional information

miR-218 precursors originate from two loci in human genome. miR-218-1 and miR-218-2 that generate one identical mature sequence and respectively mapped to Slit2 15th intron on 4p15.31 and Slit3 14th intron on 5q34 chromosomal region. SLIT family are membrane-associated glycoproteins that bind to a receptor named Roundbout (ROBO)

and acts as a repulsive mediator preventing the crossing of longitudinal axons through the midline of the central nervous system of most bilaterian animal species during neural and growth development (54, 55). Slit2 is considered as a tumor suppressor gene due to its inactivation in different malignancies including breast cancer (56). Slit2 promoter region analysis in tumor cells demonstrated that reduced expression of Slit2 was correlated with hypermethylation of its CpG island in lung, breast, colorectal, glioma, kidney and neuroblastoma tumors (54,57-59). Slit2 also identified as a conserved target of beta-catenin/Wnt signaling pathway (60,61). The CpG island of Slit3 was also observed to be hypermethylated in glioma and breast tumors (57). Intronic location of miR-218 strongly suggests that precursor sequences of miR-218 are transcribed together with their host genes, and the association between expression patterns is validated in various studies (14,62). It was also showed that the concomitant transcription pattern of miR-218 precursors with their host genes, creates a negative feedback loop that regulates Slit-Robo1 signaling pathway (14).

MiR-218 in solod tumors

MiRNA-218 in esophageal squamous cell carcinoma

Esophageal squamous cell carcinoma (ESCC) is one of the most prevalent and lethal types of human cancers worldwide, particularly common in Asia. However, little is known about genetic alterations in ESCC. Specific and sensitive biomarkers for early detection are required to reduce the high mortality and morbidity of the disorder. Tumor-suppressive miRNAs seem to be good potential diagnostic and therapeutic biomarkers.

In a study delineating the expression profile of several miRNAs in a population of 138 Chinese patients newly diagnosed with ESCC,both microarray and quantitative RT-PCR data revealed that miR-218 was significantly under-expressed in tumor tissues in comparison with adjacent non-tumor tissues (18). In another study, Tian H. et al. showed that the expression level of miR-218 was significantly increased in ESCC compared with normal adjacent tissue. They also found a correlation between its expression level with clinicopathological features of samples such as tumor stage, metastasis. They also found that induced expression of miR-218 significantly reduce migration and invasion and proliferation of cancer cells and accumulated cells in G0/G1 phase (63).

MiRNA-218 in glioma

Glioma is a common type of primary brain tumor, accounting for about 33% of these tumors and the most important reason for poor prognosis of this cancer is invasive behavior of glioblastoma cells. Tumor cells must digest the cellular matrix and filter through cell margin to initiate invasion.

Compared with ESCC,larger body of studies has investigated the expression patterns of miR-218 in Glioma.In YANWEI LIU's study, IHC and FISH analysis confirmed the reverse relationship between miR-218 with LEF1, a nuclear transducer involved in Wnt signaling pathway, and also MMP9 protein level (P value =0.021 and 0.015, respectively). MMP protein family has crucial roles in invasion regulation (64). Studies on up-regulation and inhibition of miR-218 in glioma cell lines have revealed decreased and increased levels of cell invasion, respectively. In this study the expression of miR-218 was significantly down regulated in glioma tissues comparing to normal brain samples (P value =0.009). This reduction was greater in III and IV grades in comparison with II and III (I/II VS III or IV, P value = 0.021 and 0.001). This data shows that miR-218 expression level may change in different phases of cancer, and act as a multifunctional miRNA. miR-218 as an intermediary molecule can regulate the expression of MMP9 and MMP7 by targeting transcription factors involved in the Wnt signaling pathway and repress the neural cell proliferation and migration in normal levels of oxygen.Wnt signaling directly targets the MMP promoters (MMP2/9/7) through the LEF/TCF complex and stabilizeB-catenin protein (65,66). In another study Hongping Xia et al. performed luciferase reporter assay and argue thatmiR-218 can suppress NF-KP activity by targeting ECOP (Epidermal growth factor receptor-co amplified and over expressed protein) mRNA (P value <0.05) and therebysensitize the glioma cells for apoptosis (67). Further study conducted by Yanyang Tu et al, demonstrated that miR-218 ectopic expression significantly diminishes cells invasion and proliferation ability in glioma cell lines. They also utilized computational strategies to scan for the potential targets of miR-218 and validated Bmi1, a poly comb group protein, as a putative target for miR-218 by luciferase reporter technique (P value <0.01) (68). Moreover, Ashraf Dallolr et al. results indicate that the CpG island in the promoter region of Slit2, miR-218-1 precursor host gene, was hypermethylated in 71% of glioma cell lines and 59% glioma samples.

They also performed loss of heterozygosity analysis at a microsatellite marker within Slit2 and showed the allele loss in 5% of informative cases.

MiR-218 in cervical cancer

The mortality of cervical cancer is still in high levels and most of the patients diagnosed with this cancer are at late stages with regional or distant metastasis (16). Using miRNA array analyses for early and advance staged of cervical cancer tissues, in combination with sequencing verification, Long Huang et al. identified miR-218 as a discriminator for metastatic and non-metastatic cervical tissues (P value <0.005) (69). The investigation of miR-218 effect on radio sensitivity of cervical cancer was reported in 2014 by Wang Yuan. According to this report, primary cervical cancer cells with low levels of miR-218 were less sensitive to radiotherapy comparing to those with high level of miR-218 (R2=0.6471, P value <0.001). The expression level of miR-218 was also significantly down regulated in cervical cancer samples and cell lines compared with normal specimens (P value <0.001). Interestingly, over expression of miR-218 enhanced radiation induced apoptosis (P value <0.05) (70). Role of miR-218 in increasing thesensitivity of CC cells in chemotherapy was reported by Jiarui Li et al in 2012. According to this data, there is a reverse relationship between miR-218 and its target, Rictor (rapamycin-insensitive companion of mTOR), and the chemo sensitivity of CC cells is directly affected by miR-218 (P value <0.05). In addition, the transfection analysis showed that caspase group proteins activity is increased by miR-218 over expression. Moreover, this microRNA can stimulate apoptosis and decreased the proliferation rate and cells viability through AKT-mTOR signaling pathway (71). Another study by Noriko Yamamoto et al. showed that the expression level of miR-218 was significantly lower in clinical cervical cancer specimens and cell lines than in non-cancerous samples (P value=0.0026 and P value=0.0001 respectively). In this study, LAMB3, an important part of basal lamina, shows a reverse relationship with miR-218 at both mRNA and protein levels and was introduced as one of the direct targets of miR-218 (P value=0.0461). By contrast, the expression level of LAMB3 is high in tumor samples compared with normal tissue (P value=0.0104). The group also introduced Focal adhesion pathway as involved signaling pathway in this relationship (72).

MiR-218 in gastric cancer

Gastric cancer (GC) is the second leading cause of cancer mortality worldwide (73). Ying Shi et al. showed that TFF1 (a member of Trefoil peptide family correlated with tumorigenesis) has a potential target sequence for miR-218. Western blotting and mRNA expression analysis showed opposite expression pattern between miR-218 and TFF1, but the remarkable result is up regulated expression of miR-218-5p in tumor samples compared with normal (P value =0.01). Additional analysis showed that miR-218-5p can control the progression of GC via TFF1 and ERK1/2 dependent pathways (74). In contrary to this data, Caiping Gao et al. demonstrated that miR-218 expression is significantly lower in gastric cancer samples than in their paired normal tissues (P value <0.01). They performed a luciferase reporter assay to validate the direct targeting of ECOP (Epidermal growth factor Co-amplified and over expressed Protein) by miR-218 (P value <0.01). ECOP is a key regulator of Nf-KB signaling and miR-218 inhibits nuclear factor kappa B activation by decreasing ECOP (75). In a report by Jun Tie et al. the possible process for GC metastasis has been described. They demonstrated that the expression of two precursor genes for miR-218 (miR-218-1 and miR-218-2) correlates with expression of their host genes (Slit2 and Slit3, respectively). Furthermore, they reported thatthe reduction of Slit3 in GC metastasis cells (compared with normal gastric tissue) (P value=0.0001), directly reduces the mature miR-218, whereas Slit2 expression has no significant effect (P value =0.0772). So it seems that the mature form of miR-218 is largely derived from miR-218-2 precursor in Slit3 host gene. They also evaluated ROBO1 mRNA and protein level after miRNA over and under expression and reported an inverse relationship between miR-218 and ROBO expression in the cell (P value <0.05). ROBO can interact with Slit and promote tumor angiogenesis and metastasis via over expression in cancer cells. They also found an association between decreased expression of miR-218 in GC and advanced clinical stage, lymph node metastasis and poor prognosis (P value<0.05) (14). Additionally, serum level of miR-218 in GC patients is decreased compared to normal serum (P value=0.026). Moreover, serum level of miR-218 was found to be associated with tumor progression features such as metastasis, tumor T stage and grade (P value=0.003, P value=0.018 and P value=0.012, respectively) (76).

MiR-218 in prostate cancer

Prostate cancer is the most common cancer in men and second cause of mortality in western countries. In a study, Katia RM Leite et al. attempted to compare miR-218 expression level in two sample groups of localized high grade prostate carcinoma (PC) and metastatic samples. In summary, miR-218 was invariably highly expressed in all localized high grade samples compared to metastatic carcinoma samples and PC cell lines (P value<0.001) (26). They also demonstrated that miR-218 was over expressed in all high grade PC samples compared with benign prostate tissue (P value<0.001). Additionally, miR-218 illustrated a shift in expression between high grade PC and localized invasive adenocarcinoma and there was a significant loss of miR-218 related to transition from localized to metastatic adenocarcinomas (77).

MiR-218 in lung cancer

Lung cancer is one of the leading causes of cancer related death in western countries (78). In a study conducted by Cathie Carnis et al. it was shown that large alterations such as loss of 5q, host region for miR-218-2, is common in lung cancer specimens (79). Five years later, Morgan R. Davidson et al. for the first time identified the location of miR-218 as a putative tumor suppressor miRNA in lung cancer within a region of genomic loss (4p.15.31 and 5q35.1). They also measured the expression level of miR-218 and its host genes Slit2 and Slit3, in their array CGH training set and paired normal lung. In their study, the expression of Slit 2 and Slit3 were significantly down regulated in tumor samples compared to normal tissues (P value<0.001), but there was nosignificant relationship between host gene expression level and its copy number. MiR-218 was significantly correlated only with slit2 but not Slit3 (P value=0.03 and P value=0.05, respectively). This may reflect irregular production of miR-218 from each loci, alteration of miR-218 biogenesis process or existence of separated promoters from host genes (80). In combination with Real-time PCR and immunohistochemical analysis De-Wei Wu et al. identified significant reverse relationship between miR-218 and PXN (Paxillin), the focal adhesion protein. There was a positive correlation between both PXN mRNA and protein expression in lung tumors with tumor stages (PXN mRNA, P value=0.022; PXN protein, P value=0.035). Authors showed that high expression of PXN was more prevalent in stage III compared to stagesII and I. Conversely, the high expression of miR-218 in stage III was less prevalent of that in samples at stages II and I. Furthermore, their Kaplan-Meier analysis showed that the patients with higher levels of miR-218 expression have longer average months of Overall Survival (OS) and Relapse Free Survival (RFS) comparing to the patients with lower levels of miR-218 (26.0 months vs. 33.9 months, P value =0.014 for OS; 19.3 months vs. 35.4 months, P value =0.011 for RFS) (81). One considerable cause for lung cancer related morbidity is brain metastasis. Althoughthe molecular mechanism for brain metastasis is not yet clearly understood, it seems that there is an important relationship between CDH2 (N-Cadherin, a mesenchymal marker for epithelial-mesenchymal transition) and ADAM9 (a type I trasmembrane protein) regulation and brain metastasis in lung cancer. Yuh-Ping Sher et al. demonstrated that ADAM9 expression was significantly up-regulated in aggressive lung adenocarcinoma cells and could activate the expression of CDH2 (P value<0.05). In order to gain molecular insights into the role of miR-218, above mentioned group performed a luciferase assay and western blot analysis to show that CDH2 is one of target genes for miR-218 and there is a reverse relationship between them (P value<0.05). Additionally their quantitative RT-PCR results showed that in contrast with CDH2, the expression of miR-218 was significantly lower in aggressive and metastatic lung cancer cells. They examined precursor expression levels to investigate which miR-218 precursor is really deregulated in aggressive lung cells. They concluded that down-regulation of mature miR-218 expression is directly correlated with Slit2 host gene as well as miR-218-1 precursor, and there was no significant relationship with Slit3 and miR-218-2 precursor (82). It is known that Slit2 could regulate beta-catenin and suppress cell migration (83). However it was shown that down-regulation of miR-218 was associated with low expression levels of Slit3 in gastric and thyroid cancer (23,62). These expression alterations between different tissues may be due to tissue specificity for miR-218 precursor expression. In a MTT assay conducted by Cailian Zhang et al. it has been shown that miR-218 over expression had no effect on cell growthand viability rate inmalignant lung cells (P value<0.01). They suggested that miR-218 can play an important role in lung metastasis by reduction of migration and invasion ability of cancer cells (P value<0.001). They also confirmed direct targeting of HMGB1 (High Mobility Group Box 1) by miR-218 and an inverse

relationship between them (P value<0.05). They showed that restored expression of HMGB1 could increase cell migration and invasion ability, reduced by miR-218 mimics (84).

MiR-218 in colorectal cancer

Colorectal cancer (CRC) is the third major cause of cancer related mortality (73). Using Real-time PCR analysis Hong Yu et al. showed that miR-218 expression level is down regulated (in consistent with its host genes) in CRC tissue and serum samples compared to normal adjacent tissue and normal blood (P value <0.001 and P value <0.05 respectively). MiR-218 expression with respect to Patients characteristics also showed a connection between low expression level of miR-218 with high TNM stage of samples and worse survival (P=0.038 and 3.9 *10-4, respectively) (15). Additionally Whole-genome loss of heterozigosity analysis revealed the association of significant loss of Slit2 expression with promoter methylation of Slit21 in CRC samples (85). Xinqi He et al. identified BMI1 (polycomb ring finger oncogene-1) as one of the potential targets for miR-218. The expression level of miR-218 showed significant down regulation in CRC samples compared with normal tissue, and BMI1 expression analysis exhibited a significant inverse correlation with miR-218 expression (P value=0.001, r=-0.823, P value <0.01). They further revealed that miR-218 up-regulatesp 53 protein expression while suppressing the expression of BMI1 protein which is a downstream target of cell cycle regulator, Cyclin-Dependent-Kinase 4. This suppression can result an increased number of accumulated cells in the G2 phase (P value=0.01). Unexpectedly, they reported that there is not any correlation between miR-218 expression and clinicopathological characteristics of patients such as tumor stage and recurrence (86).

MiR-218 in pancreatic cancer

Pancreatic cancer is one of the major causes of cancer related morbidity worldwide. Ziman Zhu et al. reported asignificant relationship between low levels of miR-218 in PDAC cells and tissue samples, and poor tumor differentiation, advanced tumor stage, higher incidence of lymph node metastasis, tumor recurrence and lower 5 year RFS (P value=0.002, 0.001, 0.002, 0.010 and 0.009 respectively) (87). In another research, CHI HAN LI et al. performed quantitative RT-PCR and immunohistochemistry analysis and showed that levels of miR-218 is significantly lower in primary PDAC tumor samples compared with paired adjacent normal tissue (P value <0.0001). Additional experiments approved that EZH2 (Enhancer of Zeste Homolog2) is capable to silence miR-218 expression by histon methylation and heterochromatin modification of its promoter. As miR-218 target genes, highly expressed levels of UTG8 (UDP glycosyltransferase) and VOPP1 (over expressed in cancer, prosurvival protein) were also observed to be significantly associated with dysregulation of EZH2-miR-218 pathway and increased cell aggressiveness. They also evaluated Slit2 and Slit3 levels, and showed that only expression of Slit3, not Slit2 was low in pancreas cancer cell lines (P value <0.05). Conclusively, they reported that levels of mature miR-218 were totally associated with miR-218-2 precursor and Slit3 host gene expression and promoter methylation (P value <0.05) (88).

MiR-218 in hepatocellular carcinoma

Hepatocellular carcinoma is the fifth most common malignancy worldwide (89). Zhong-Di Xiao et al. investigated the molecular mechanism of miR-218 regulatory pathway in human hepatocellular carcinoma (HCC), and showed that tumorigenesis related proteins cyclin D1 and p21, together with PTEN/AKT/PI3K signaling pathway are connected to miR-218. Additionally, they suggested that due to the reverse correlation between miR-218 and HOXA10, this protein is directly associated with miR-218 in regulating PTEN/AKT/PI3K pathway in HCC cells. They also reported that miR-218 expression is down regulated in HCC cell lines and tissue samples compared with normal cells and paired tissues (P value <0.05) (90). Down regulation of miR-218 in HCC cell lines and tissue samples was also reported by Chengjun Sui et al. (Pvalue <0.05). They combined bioinformatics analysis and functional assays to predict and confirm that miR-218 is directly targeting RET (a transmembrane receptor-type tyrosin kinase and functions as proto-oncogene) in HCC cells. They showed that the protein level of RET was also up regulated through miR-218 transfection (P value <0.05) that could reverse the anti-proliferative effect of miR-218 upregulation, whereas the expression of PTEN (phosphatase and tensin homolog deleted on chromosome 10, a tumor suppressor gene and targets of mTOR signaling pathway in cancer) was significantly down regulated (P value <0.05) (91).

MiR-218 in thyroid cancer

Thyroid cancer is the most common malignancy of endocrine system and its overall incidence and mortality is increasing rapidly in recent years worldwide (92). In a study by Hongyu Guan et al. statistical analysis of expression levels of pre-miR-218-1 and Slit2, pre-miR-218-2 and Slit3 showed that microRNA transcripts positively correlated with their related host genes (P value <0.05). QRT-PCR analysis also showed that miR-218 expression is down regulated in thyroid cancer lesions compared to normal tissue (P value <0.05), but it wasn't observed any association between down regulation of miR-218 and the degree of malignancy phenotype. Moreover, they suggested that expression levels of mature miR-218 in thyroid cancer attributes to miR-218-2 precursor and Slit3 host gene (P value <0.001); Whereas, no significant difference was observed in Slit2 expression level in thyroid cancer specimens compare with normal tissue (P value =0.995). According to this data and additional analysis, it seems that miR-218-2 and Slit3 have a functional relevance in invasion and proliferation of thyroid cancer cells. Furthermore, bioinformatics and functional analysis demonstrated two direct targets of miR-218-2, PDGFRA (platelet-derived growth factor receptor, which is a cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family) and PLCG1 (phospholipase C, which plays an important role in the intracellular transduction of receptor-mediated tyrosine kinase activators) which both of them are involved in cancer cell invasion and mitosis (62).

MiR-218 in melanoma

The most fatal form of skin cancer is cotaneous melanoma, and its incidence has increased recently worldwide (93). In a study, Hun-Way Huang et al. investigated the expression levels of miR-218 precursors and HIF1A (hypoxia inducible factor 1 alpha) and found a positive correlation between miR-218 and HIF1A over expression in melanoma cell lines (P value<0.05). Moreover, the expression of miR-218 was significantly decreased by HIF1A suppression (P value<0.005). Expressional analysis for Precursor sequences also showed that there was specificity for the pri-miR-218-2 locus on Slit3, because the down regulated sequence of miR-218 is attributed to pri-miR-218-2 which was decreased by 70%, while pri-miR-218-1 was unaffected (94). Expressional analysis conducted by Yanping Wei et al. showed that the expression levels of miR-218 were down regulated in primary and metastatic melanoma samples and cell lines compared with normalspecimens (P value<0.05). Moreover CIP2A (cancerous inhibitors of protein phosphatase 2A,) and BMI1, two cellular oncogenes, were in a reverse relationship with miR-218 expression (P value <0.05) and according to luciferase assay data, they are targeted by miR-218 directly in their 3-UTR region. Additional cell line experiments showed that miR-218 inhibited cell proliferation and arrest cell cycle in G0/G1 phase and significantly reduced the percentage of cells in S phase (P value <0.05) (95). Differential expression of miR-218 in acral melanoma compared to non-acral melanoma makes it a possible biomarker to distinguish between melanoma subtypes (96).

MiR-218 in renal carcinoma

Renal cell carcinoma (RCC) is the most common cancer of the adult kidney (97). Renal carcinoma tumors originate from kidney parenchyma and the incidence of this cancer is low in Asia and South America in contrast with Europe and North America (98). According to luciferase reporter assay performed by Takeshi Yamasaki et al. CAV2 (Caveolin2) a gene involved in Focal adhesion pathway, has an actual target region in its 3-UTR for miR-218. Expressional experiments also showed that there was an inverse correlation between miR-218 and CAV2 expression levels (r=-0.58, P value<0.0001). MiR-218 was significantly down regulated in RCC samples and cell lines compared to normal (P value<0.0001) (99). Slit2 promoter methylation has been previously described by Ashrad Dallol et al. in RCC samples and cell lines. However it seems that the original resource of mature form of miR-218 is Slit2 host gene and miR-218-1 precursor in RCC considering consistent expression levels of this miRAN with Slit2 host gene (59). In addition, tumor suppressory roles of miR-218 in RCC cell lineshas been revealed through functional screening analysis conducted by Hideo Hidaka et al (100).

MiR-218 in nasopharyngeal carcinoma (NPC)

Nasopharyngeal carcinoma is associated with Epstein-Bar virus and has a high incidence in East Asia and Africa. In the only study that was published regarding the expression pattern of miR-218 in NPC tumors, it was reported that the expression of miR-218 and its host genes are consistently down regulated in NPC samples and cell lines compared

with normal cells (P value<0.0005). Additional investigations indicated that epigenetic modifications such as hypermethylation of Slit3 and Slit3 host genes promoter's leads to under expression of Slit2 and Slit3 genes and subsequently miR-218 down-regulation in different malignancies. Moreover, luciferase reporter assay analysis also resulted in identification of direct interaction between miR-218 and 3-UTR region of BIRC5, ROBO1, and GJA1mRNAs. ROBO1 has an inverse correlation with patient's OS (overall survival) and (23) plays important role in cell invasion and migration (55,101).

MiR-218 in medulloblastoma

Medulloblastoma (MB) is one of the most common forms of brain and cerebellar related tumors in children (102). High throughput miRNA microarray and RT-PCR expressional analysis performed by Liu Wei et al. validated down regulation of miR-218 expression levels in primary MB specimens compared to normal tissue (P value=0.004) (103). In a study conducted by SujathaVenkataraman et al. the expression of miR-218 was observed to be down regulated in MB cell lines and samples compared with normal cells (P value<0.0001). Additional in vitro experiments also showed that induced over expression of miR-218 reduces malignant features of medulloblastoma cells. Moreover, an inverse significant correlation was observed between miR-218 with CDK6 (cyclin dependent kinase 6), RICTOR (rapamycin independent companion of mTOR) and CTSB (cathepsin B) expression levels (104). In another study,Jipeng Shi et al assessed and validated reverse relationship between miR-218 and SH3GL1 in MB cell lines and samples by qRT-PCR, luciferase reporter assay and western blotting analysis. Authors performed additional analyses to clarify miR-218 and SH3GL1 associated signaling pathways in MB. They revealed that miR-218 mediates SH3GL1 via MAPK signaling pathway (P value <0.05) (105).

MiR-218 in bladder cancer

Bladder cancer (BC) is the second most common genitourinary related cancer (106). To appraise genomic aberrations in BC, R Matsuda et al. performed CGH-array analysis on BC cell lines. They reported that one of the loci which most frequently undergoes genetic lostin BC is on chromosome 4p where miR-218-1 Precursor is located (107). In another study, Shuichi Tatarano et al focused on chromosome 4p15.31 and miRNAs located in this region. They validated CGH-array data by evaluating the expression level of miR-218 and found a significant down regulation in all four BC cell lines. Additional gain of function studies also showed significant cell proliferation inhibition in miR-218 transfectant cell lines (P value<0.05). They also predicted one of potential targets of miR-218 named TMX1 (25). Additional investigations showed that there is a reverse correlation between miR-218 and LASP1 (LIM and SH3 protein 1) mRNA and protein levels, introducing LASP1 as another target of miR-218 (108).

MiR-218 in breast cancer

Breast cancer is the most common diagnosed cancer and major cause of cancer related morbidity in women (109). Aoife J Lowery et al by using artificial neural networks (ANN) combined with miRNA expression profiling and qRT-PCR analysis, showed that miR-218 has a distinct expression pattern for discriminating between ER-positive and ER-negative breast tumors with accuracy of 100% (110). Qiaoyan Li et al demonstrated that expression of HoxB3 (highly conserved subgroup of the homeobox family) is strongly and reversely in correlation with miR-218 and this miRNA works synergistically with miR-7 to target HoxB3 3'-UTR. They also constructed stable miR-218 expressing breast cancer cell lines and showed that in these cells tumor suppressor genes, RASSF1A (RAS associated domain family 1A) and CLDN6 (Claudin 6) mRNA levels are significantly increased, resulting in inhibited cell cycle and colony formation of breast cancer cells (P value <0.05) (111). According to Mohammad Q. Hassan et al study, miR-218 directly regulates osteogenesis-related signaling pathways such as Wnt and BMP and may mediate progression of osteogenesis pathways. By using luciferase reporter assay analysis during bone formation, they validated fourWnt signaling pathway negative regulators as miR-218 targets namely, Tob1, Dkk2, sfrp2 and Sost. They also found that induced expression of miR-218 actively increased endogenous Tcf-1 and Lef-1 expression levels and endogenous Wnt was highly activated in metastatic breast cell lines. Expressional analysis showed that miR-218 expression is low in mammary epithelial normal cells while it is increased by 10 fold in highly metastatic cells. Conclusively, they found that miR-218 induces expression of Wnt activators like TCF-1, B- catenin, Runx2 by suppressing expression of inhibitors such as axin2 (112). In another study, Xiao

He et al. showed that miR-218 is down regulated in cisplatin-resistant breast cancer cells. MTS and colony-forming assays represented significant increase in IC50 in mir-218 transfectant breast cancer cell lines after cisplatin treatment. They also validated targeting of BRCA1 (breast cancer 1) 3-UTR, DNA repair gene, by miR-218. Diverse strategies was used in this study to show that low expression of miR-218 and high expression of its target, BRCA1, are associated with cisplatin resistance and cell viability in breast cancer cell lines (113). Tatiana Y Prudnikova et al investigated the correlation between miR-218 and GLCE (D-glucuronyl C5-epimerase) tumor suppressor gene, in breast cancer cells. They observed a significant decrease of miR-218 expression level in primary breast tumors. They also found an inverse correlation between miR-218 and GLCE protein levels but not mRNA, indicating possibly incomplete interaction between miR-218 and GLCE mRNA which only results in suppression of mRNA translation (114).

Discussion and Conclusion:

First discovered in 2012 by Sempere LF et al (13), miR-218 has been implicated to prevention of various types of cancers as a tumor suppressor miRNA; however, further studies argued that It can also have other regulatory functions in cancerous cells including oncogenic role as its over-expression was observed in some other types of cancer or specific conditions such as higher grades and stages of the disease (26,63,74, 77,110). Despite such controversial observations, several studies have proposed the association of miR-218 expression perturbation with poor prognosis in some malignancies (14-16,69).

Here, an attempt was made to decipher the precise molecular role of miR-218 in various solid tumors. To do so, we reviewed up to 124 original articles regarding to functional analysis of miR-218 during tumorigenesis or development of different solid malignancies. Many of these studies were aimed to investigate expression level of miR-218 in corresponding cell lines or tumor tissues accompanied by experimentally validated methods in order to confirm dysregulated miR-218 target genes and signaling pathways. However, we also reviewed the studies aiming to only examine expression pattern of miR-218 in diverse biological samples derived from various solid malignancies.

Table 1 and figure 1 represent a brief summary of miR-218 functions in different solid tumors. As it is evident, majority of studies propose the tumor suppressor role of miR-218 during tumorigenesis of different solid tumors considering the fact that it is significantly down-regulated in tumor tissues in comparison with normal healthy specimens. In addition, in all of these studies it is shown that in-vitro ectopic over-expression of miR-218 contributes to suppression of cell proliferation, metastasis and invasion by targeting various oncogenic proteins (Figure 1). By contrast, two studies represent oncogenic role of miR-218 during tumorigenesis of cancerous cells in Gastric cancer and Esophageal Squamous Cell Carcinoma by providing concrete in-vivo and in-vitro evidence (63,74). These studies demonstrated that miR-218 is up-regulated in tumor tissues compared with normal tissues. Furthermore, functional analysis revealed that ectopic induction of miR-218 in cancerous cell lines results in increased cell proliferation by targeting TFF1 protein (74) (Figure 1). In consistent with these data, comparison of miR-218 expression level among tumor tissues with different grades and metastatic stages, showed that expression of miR-218 is elevated in first and middle grades compared with higher grades where cancerous cells acquire metastatic and invasive characteristics (26,77,110). Likewise, recently we analyzed expression level of miR-218 in 33 pairs of breast tumors and adjacent normal tissues. Our results revealed up-regulation of miR-218 in cancerous tissues compared with normal adjacent tissue; however, it was significantly down-regulated in Lymph node metastatic (LNM) positive compared with LNM negative samples (F Ahmadinejad et al, Shahrekord University of Medical Sciences, ahead of print). Finally, another set of studies attributed different functions to miR-218 in cancerous cells, represented its role in chemo sensitivity to Cisplatin and promoting osteomimetic properties in metastatic cancer cell by targeting BRCA1 and Sclerostin/ Dikkopf2, respectively (112, 113) (Figure1).

Taken together, the studies highlighted in current review clearly indicate that miR-218 act as a multi-functional regulator of cellular processes in cancerous cells and its expression perturbation could be representative of various states of the solid tumors. In fact, considering cancer as a complex and multi-state disease, it seems that miR-218 function as a Double-edge sword in solid tumors where despite its tumor suppressive role, its expression at a basic level is required for regulation of cancerous cell proliferation

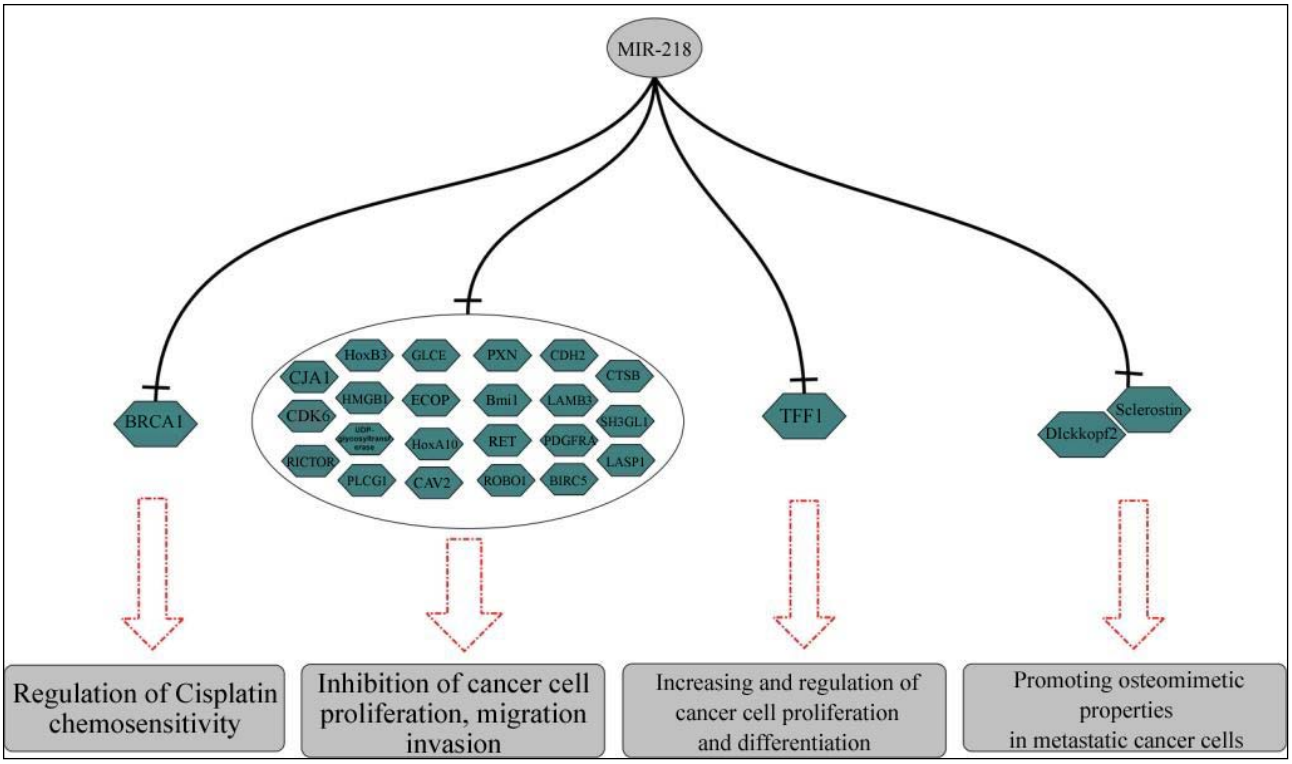

Figure 1: Various functions of miR-218 in solid tumor cells. By targeting different set of target genes in various cancerous cells, miR-218 participates in diverse functions, including Regulation of Cisplatin chemosensitivity (A), Inhibition of cancer cell proliferation, migration, and invasion (B), Increasing and regulation of cancer cell proliferation and differentiation (C), and promoting osteo-mimetic properties in metastatic cancer cells (D).

BRCA1: Breast Cancer1, GJA1: Gap Junction protein Alpha1, CDK6: Cyclin Dependent Kinase6, RICTOR: RPTOR independent companion of MTOR, complex 2, HOXB3: Homeobox B3, HMGB1: High Mobility Group Box1, PLCG1: Phospholipase C-Gamma 1, GLCE: Glucuronic Acid Epimerase, ECOP: EGFR-coamplified and overexpressed protein, CAV2: Caveolin 2, PXN: Paxillin, BMI1: B lymphoma Mo-MLV insertion region 1 homolog, RET: receptor tyrosine kinase, ROBO1: Roundabout, Axon Guidance Receptor, Homolog 1, CDH2: Cadherin 2, LAMB3: Laminin subunit beta-3, PDGFRA: platelet-derived growth factor receptor alpha, BIRC5: Baculoviral IAP Repeat Containing 5, CTSB: Cathepsin B, SH3GL1: SH3-Domain GRB2-Like 1, LASP1: LIM And SH3 Protein 1. TFF1: Trefoil Factor 1, DICKKOPF2: Dickkopf-related protein 2. ⇩ : induction, ⊣ : inhibition.

and differentiation, particularly at early and middle states of the disease. Hence, it seems of great importance to check patient's clinico-pathological characteristics (such as stage, tumor grade, LNM status and so forth) before interpreting miR-218 expression level as a diagnostic or prognostic factor.

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Table 1: Brief summary of miR-218 functions in different solid tumors.

Type of cancer	Num	Study type	Sample type	Deregulation direction / overall function of miR-218	Targets and signaling pathways	Clinopathological categorization		Reference
						TNM Stage	Lymph node status	
Breast Cancer	1	Case-control expression study	ER⁺/ ER⁻ fresh tumor samples	Up-regulated in ER⁺Vs ER⁻ tumors	-	Stage 1 or 2A	Negative	**(111)**
	2	Cell culture functional analysis study	Stable miR-218 expressing breast cancer cell lines	Act as a Tumor suppressor Induces RASSF1A and Claudin-6	HoxB3	-	-	**(112)**
	3	Cell culture functional analysis study	MC3T3-E1 osteoprogenitors Bone marrow stromal cells MCF10A epithelial cells	Inducer of osteogenic lineage commitment and progression promotes osteomimetic properties in metastatic breast cancer cells	Sclerostin, Dickkopf2, Frizzled-related protein2 (Wnt signaling pathway inhibitors)	-	-	**(113)**
	4	Cell culture functional analysis study	MCF-7 cell line, cisplatin-resistant cell line (MCF-7/DDP)	Ectopic overexpression Rescued cisplatin-resistance in breast cancer cells	BRCA1	-	-	**(114)**
	5	Case-control expressiona I and cell culture functional analysis study	Primary breast cancer Tissue Vs normal breast tissue MCF7 cell line	Down regulated in Primary breast tumors VS normal tissues Act as tumor suppressor	GLCE	Majority of samples were Stage 2	ND	**(115)**
Lung Cancer	1	Case-control expressional study	primary non-small cell lung cancers (NSCLCs) VS Normal lung tissues	Down regulated in Primary NSCLCs tumors Act as tumor suppressor	-	ND	ND	**(81)**
	2	Case-control expressional and cell culture functional analysis study	primary lung cancer VS normal tissue Lung cancer cell lines	Down regulated in primary tumors Act as a tumor progression and metastasis suppressor	PXN	40.3% stage I 20.2% stage II 39.5% Stage III	ND	**(82)**
	3	Cell culture expressional and functional analysis study	Non invasive VS invasive lung adenocarcinoma cell lines	Down regulated in Non invasive VS invasive cells Act as a metastasis and invasion suppressor	CDH2	-	-	**(83)**
	4	Cell culture functional analysis study	Human lung cancer cell lines, A549 and H1299	Act as a metastatic and invasion suppressor	HMGB1	-	-	**(85)**
Prostate Cancer	1	Case-control expressional study	localized high grade prostate carcinoma staged pT3 Vs metastatic, androgen-independent prostate carcinoma	Up-regulated in High grade tissue Vs metastatic carcinoma Act as a metastasis suppressor	-	-	-	**(27)**
	2	Case-control expressional study	high grade prostate Vs local invasive VS metastatic tissue samples	Up-regulated in High grade Vs local invasive and metastatic samples Act as a metastatic suppressor	-	-	-	**(78)**
Esophageal Squamous Cell Carcinoma	1	Case-control expressional study	Primary ESCC tumor tissues VS adjacent non-tumor tissues	Down-regulated in tumor tissue VS adjacent normal tissue Act as a tumor suppressor	-	ND	ND	**(18)**
	2	Case-control expressional and Cell culture functional analysis study	Primary ESCC tissues VS matched non-tumor tissues	Up-regulated in tumor tissue VS adjacent normal tissue Act as a tumor suppressor	-	ND	ND	**(64)**

Glioma	1	Cell culture functional analysis study	Human glioma cell lines (U87, U118, U138, U373, SW1088, SW1783) VS immortalized glial cells	Down regulated in Glioma cell lines VS Glia cells Act as a tumor suppressor	ECOP NF-kB signaling pathway	-	-	**(68)**
	2	Cell culture functional analysis study	Human glioma cell lines	prevents migration, invasion, proliferation of Glioma Cells Act as a tumor suppressor	Bmi1	-	-	**(69)**
Cervical Cancer	1	Case-control expressional study	Formalin-fixed paraffin-embedded tissues (FFPETs)	Its downregulation correlates with metastatic parameters Act as a tumor suppressor	-	Staged 1A and 2	31% positive and 68% negative	**(70)**
	2	Case-control expressional and Cell culture functional analysis study	fresh cervical cancer VS non-cancerous cervix tissues tumor dereived cell culture	Down-regulated in cancer tissue VS normal samples Promotes radio-sensitivity in patients	-	ND	ND	**(71)**
	3	Cell culture expressional study	human cervical cancer cell line HeLa	Overexpression of miR-218 reduced the proliferation of the human cervical cancer and increased chemosensitivity to cisplatin Act as a tumor suppressor	-	-	-	**(72)**
	4	Case-control expressional and Cell culture functional analysis study	primary cervical SCC specimens VSnon-cancerous specimens Cervical SCC cell lines	Down-regulated in SCC VS non-cancerous Inhibits proliferation, migration and invasion	LAMB3	-	-	**(73)**
Gastric Cancer	1	Case – control expressional and cell culture functional analysis study	GC patient tumor lesions VS normal paracancerous tissue samples BGC-823 and SCG-7901 cell lines	Up-regulated in tumor tissue VS normal tissue Act as an oncogen Increases and regulates proliferation	TFF1 Erk1/2 signaling pathway	-	-	**(75)**
	2	Case-control expressional study	serum of gastric cancer patients VS healthy individuals	Down-regulated in Patients VS Healthy specimens More reduction in patients with metastasis	-	ND	ND	**(77)**
Colorectal cancer	1	Case-control expressional study	CRC tissue and serum sample VS normal adjacent tissue and normal serum	Down-regulated in patients VS healthy specimens Diagnostic and prognostic Biomarker of Lymph node metastasis	-	12.7% staged I 38.6% staged II 42.9% staged III 5.5% staged IV	55% negative 45% positive	**(15)**
	2	Case- control expressional and cell culture functional analysis study	primary tumor VS adjacent non-tumor tissue Colon cancer cell lines HCT116, HT29, SW620 and LoVo	Down-regulated in tumor tissue VS normal adjacent tissueAct as a tumor suppressor Ectopic expression induces apoptosis and inhibit cell proliferation and promotes cell cycle arrest at G2	BMI-1	-	-	**(87)**
Pancreatic cancer	1	Case-control expressional study	Pancreatic ductal adenocarcinimat tissues VS normal pancreatic tissues	Down regulated in tumor tissue VS normal tissue Reduced expression was correlated with poor tumor differentiation, advanced tumor stage, higher incidence of lymph node metastasis, and tumor recurrence	-	NA	NA	**(88)**
	2	Case-control expressional and cell culture functional study	primary PDAC tumor VS adjacent non-tumor tissue SW1990 cell line	Down-regulated in Tumor tissue Vs normal tissue Ectopic overexpression reduced proliferation and tumor formation and metastasis in nude	UDP-glycosyltransferase	ND	ND	**(89)**

Hepatocellular carcinoma	1	Cell culture functional study	HCC cell lines	Act as Tumor suppressor Ectopic overexpression decreased cell proliferation	HoxA10 through PTEN/AKT/PI3K pathway	-	-	**(91)**
	2	Case-control expressional and cell culture functional study	primary HCC tissues Vs adjacent non-carcinoma tissues HCC cell lines MHCC97L and Huh7	Down-regulated in tumor tissues Vs normal tissues Ectopic overexpression decreased cell proliferation andinvasion capability	RET	ND	ND	**(92)**
Thyroid cancer	1	Case-control expressional study	normal Vs neoplastic human thyroid tissues Human thyroid cancer cell lines WRO and 8305C	Down-regulated in tumor tissue Vs normal tissues Ectopic overexpression reduced the rate of proliferation, invasiveness and migration	PDGFRA and PLCG1	ND	ND	**(63)**
Melanoma	1	Case-control expressional and cell culture functional analysis study	Melanoma tissues Vs normal tissue Melanoma cell lines A375 and SK-MEL-2	Down-regulated in melanoma Vs normal tissue Ectopic overexpression reduced proliferation, migration, and invasion	CIP2A and BMI1	ND	ND	**(96)**
Renal cell carcinoma	1	Cell culture functional analysis study	A498 and 786-O renal cell carcinoma cell lines	Ectopic overexpression inhibited proliferation, migration and invasion	CAV2	-	-	**(100)**
	2	Case-control expressional and cell culture functional analysis study	Cancer Vs adjacent non-cancerous tissue RCC cell lines: A498, 786-O, ACHN and caki-2	Down-regulated in Cancer Vs normal tissue Ectopic overexpression inhibited proliferation	-	-	-	**(101)**
nasopharyngeal carcinoma (NPC)	1	Case-control expressional and cell culture functional analysis study	Primary Nasopharayngeal carcinoma tissue Vs normal tissue Nasopharayngeal carcinoma cell lines	Down-regulated in cancer Vs normal tissue Exogenous expression delayed tumor growth	ROBO1, survivin (BIRC5) and connexin43 (GJA1)	ND	ND	**(23)**
medulloblastoma	1	Case-control expressional study	human primary medulloblastoma tissue Vs on-tumorous cerebellum tissues	Down-regulated in Cancer Vs normal tissue	-	ND	ND	**(104)**
	2	Case-control expressional and Cell culture functional analysis study	human primary medulloblastoma tissue Vs on-tumorous cerebellum tissues	Down-regulated in Cancer Vs normal tissue Ectopic overexpression decreased medulloblastoma cell growth, cell colony formation, cell migration, invasion	CDK6, RICTOR, and CTSB (cathepsin B)	ND	ND	**(105)**
	3	Cell culture expressional and functional analysis study	Medulloblastoma cell lines Daoy, D458, PFSK and UW228 Vs normal cerebellum	Down-regulated in cancerous cell lines Vs normal cell lines Ectopic overexpression suppressed cell growth, migration and invasion	SH3GL1	-	-	**(106)**
Bladder cancer	1	Case-control expressional and Cell culture functional analysis study	cancerous Vs normal bladder epithelium Human BC cell Lines: T24 , UMUC, kk47, BOY.	Down-regulated in cancerous tissues Vs normal tissues Ectopic overexpression inhibited BC cell proliferation, migration and invasion.	ND	ND	ND	**(25)**
	2	Cell culture functional analysis study	Human BC cell Lines	Ectopic expression inhibited cell viability	LASP1	-	-	**(109)**

(ND = Not determined)

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