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CHARACTERIZING THE ROLE OF MIRNA IN CANCER WITH SPECIAL REFERENCE TO BREAST CANCER, LUNG CANCER AND COLORECTAL CANCER

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ABSTRACT
In recent years, there has been a tremendous and growing interest among researchers to investigate the role of microRNA (miRNA) in normal cellular as well as in disease processes. miRNAs are short, noncoding RNAs with a length of ~22 nucleotides that negatively regulates target miRNAs. miRNAs cover an important role in all biological processes, including development, cell differentiation, proliferation and apoptosis. Aberrant miRNAs expression commonly associated with cancer. In this review, we discussed how miRNAs influence tumorigenesis by acting as oncogenes and tumour suppressors. Here we also discussed the role of miRNAs in cell cycle regulation. The control of cell proliferation by miRNAs is well established and the alteration of these small, non-coding RNAs may contribute to tumor development by perturbing critical cell cycle regulators. Oncogenic miRNAs may facilitate cell cycle entry and progression by targeting CDK inhibitors or transcriptional repressors of the retinoblastoma family. On the other hand, tumor suppressor miRNAs induce cell cycle arrest by downregulating multiple components of the cell cycle machinery. Recent researches also demonstrate that miRNAs also affect many apoptosis pathway. Indeed, it is becoming clear that many miRNAs are anti-apoptotic and mediate this effect by targeting pro-apoptotic mRNAs or positive regulators of pro-apoptotic mRNAs. Conversely many pro-apoptotic miRNAs target many anti-apoptotic miRNAs. In this review we also focused on three types of cancers like breast cancer, lung cancer, and colorectal cancer are the leading cause of cancer related death. Here we summarize the functions of small-RNA-based, posttranscriptional gene regulators, i.e. microRNAs, in the pathogenesis of cancers. We also discuss the miRNAs play oncogenic as well as tumour suppressor role. Here we also demonstrated the value of miRNAs as marker for diagnosis, prognosis and the promising field of miRNA-based novel therapies cancers.

KEYWORDS: MiRNA, apoptosis, oncogenes, cancer.

1. INTRODUCTION
MicroRNAs (miRNA) are small, non-coding RNAs which regulates gene expression at post transcriptional level.[1, 2] The first discovered miRNA, lin-4 was isolated from *Caenorhabditis elegans*.[3, 4] Around 2000 miRNA have been identified in wide array of organisms including plants, zebrafish, mouse and human.[4] Mature miRNAs are generally ~22 nucleotides long.[1-4] MiRNA plays an important role in several biological processes such as cell differentiation, proliferation, and apoptosis.[1] MiRNA regulates the expression of various oncogenes or tumor suppressor genes.[1] Genes of miRNA are transcribed by RNA polymerase ll to form primary miRNA which is large in size.[5] This process is held in the nucleus.[6, 7] Then RNaselll enzyme, Drosha processed these primary miRNA and form precurssor miRNA which is 70 nucleotides long. Precurssor miRNA (Pre miRNA) transported to the cytoplasm by RAN-GTP and exportin5.[8] Another RNase lll enzyme, Dicer which processed the precurssor miRNA and formed ~22 nucleotide miRNA-miRNA complex.[2,4,5] This complex is incorporated to the RNA induced silencing factor (RISC), which is a multiprotein and also a ribonucleoprotein.[9] It belongs to the Argonate protein family.[9] Then mature single stranded miRNA binds to the target mRNA at complementary site and negatively regulate gene expression.[2, 5, 6] MiRNAs are involved in cancer initiation and progression. The expression patterns of these MiRNA can be used for classification, diagnosis and prognosis of human malignancies. Alterations of miRNA genes lead to play a critical role in human cancer.[10]

Tumor formation is positively correlated with the reduction of the amount of miRNA. It was reported that formation of human tumor is associated with the reduction of the Dicer expression levels.[12-15] In contrast, over expression of Dicer may results in the formation of

prostate cancer.[16] In addition microsatellite instability during frame-shift mutation have been reported in TARBP2, a Dicer stabilizing protein, in gastric and colorectal cancer.[12] Propagation of Drosha expression can cause oesophageal cancer.[17, 18] Apoptosis, another important cellular mechanism is associated with cancer. Apoptosis is a process to sort out cells which are transformed and damaged. Deregulation of apoptosis may results in cancer progression. As cancer cells are mainly characterized by increased cell proliferation and decreased cell death. Cancer associated genes are divided into two groups, oncogenes and tumor suppressor genes. oncogenes upregulate the cell proliferation and downregulate the apoptosis but tumor suppressor genes perform just the opposite function.[20] Another type of gene, pro-apoptotic gene such as p53 is inactivated until antiapoptotic gene such as B-cell chronic lymphocytic leukaemia (CLL)/lymphoma 2 (BCL2) are over activated during cancer progression. Thus, the role of miRNA is very crucial and complicated because it regulates both proliferation and apoptosis.[19]

Here, in this review, we have discussed about the proapoptotic miRNAs, antiapoptotic miRNAs and miRNAs to understand the interaction and involvement of these miRNAs in cancer formation. With that the role of microRNA in breast, lung, and colorectal cancer, have been discussed. We have also informed about the therapeutic measures to control the cancer.

2. Biogenesis of miRNA

The biogenesis of most animal miRNAs share a common mechanism. Mature miRNAs are formed from long primary transcripts through several biochemical processes. Generally primary miRNA transcripts are transcribed by RNA pol II and it contains 5′ caps and 3′ poly A tail, whereas some other primary miRNA (pri-miRNA) transcripts are transcribed by RNA pol III.[18] In nucleus the primary miRNA is processed to precuessor miRNA (pre-microRNA) by Drosha and DiGeorge Syndrome critical region gene 8 (DGCR8), which is class 2 RNase III enzyme.[20-25] Accroding to domain organization RNaseIII proteins are grouped into three classes.[26] In bacteria and yeast class I proteins include RNaseIII proteins are found. Each of them contains one RNaseIII domain (RIIID) and one double stranded RNA [dsRNA] binding domain [dsRBD].[26] One of the class II proteins such as Drosha exert two RIIIDs and dsRBD. The pre-miRNA is 60-80 nucleotides long.[27] The pre-miRNA is transported into cytoplasm by transport factor Exportin 5 and Ras dependent nuclear protein guanosine triphosphate (RAN-GTP) dependent manner.[27] In the cytoplasm the pre miRNA is further processed by cytoplasmic protein (TRBP) and formed ~22 nucleotide miRNA duplex.[27] Another class III includes Dicer homologs which are conserved in *Schizosaccharomyces pombe*, plants and animals.[26] Dicers are ~200 kDa and it contains multiple domains. Dicer has long N-terminal domain containing a DExH, RNA helicase/ ATPase domain, and also has DUF283 and the Piwi-Argonate-Zwile (PAZ) domain. PAZ domain is normally found in highly conserved proteins. And it binds to the 3′ protruding end of the small RNA. But till now the function of other domains in Dicer is not clear. Dicer has two terminals like N-terminal RNaseII domain (RIIIDa) and C- terminal (RIIIDb) both are different in their sequences and their roles. The 3′ strand is cleaved by Dicer RIIIDa and the 5′ strand of the pre-miRNA is cut by Dicer RIIIDb.[26] This miRNA duplex is loaded into the RNA induced silencing factor (RISC), RISC is responsible for gene silencing, where the mature miRNA strand is retained but complementary passenger strand is degraded by an unknown nuclease. The active component then binds to a member of the Argonate proteins that regulate the translocation of target mRNA. MiRNA binds to the 3′UTR (untranslated region) region of their complementary target mRNA and inhibit the translocation or guide the degradation of target mRNA.[27] Recent studies shows that miRNA also binds to the 5′ UTR or open reading frame of the target mRNA.[27] The overall mechanism is demonstrated in Fig 1.

3. Mutation and miRNA

MiRNA biogenesis play an important role in cancer. Defects in biogenesis pathway of miRNAs result in the modification of the expression level of miRNA. Deregulation of the enzymes and cofactors which is involved in the biogenesis pathway can affect the levels of mature miRNAs, which may have important biological classification.[18] The initiation step of the miRNA biogenesis is the transcription of pri-miRNA. In multiple human cancers this 1st step is dysregulated. At fragile sites or in genomic region a significant number of human miRNA genes are located and in cancer that miRNAs are deleted, amplified and translocated. These genomic variations may lead to alteration of pri-miRNA transcription and miRNA expression causes downstream expression of mRNAs which promote cancer initiation and progression.[28-30] For example miRNA-15 and miRNA-16 is located on chromosome 13q14 which is frequently deleted in B-cell chronic lympholytic leukaemia(B-CLL). For that reason the number of these two miRNAs is reduced in~ 70% of BCLLs. These miRNAs 15-16 control the apoptosis by targeting B-CLL2 mRNAs.[31] In another point mutation in the miRNA 128b gene which blocks the processing of pri-miRNA 128b and also loss the expression level of mature 128-b may leads to glucocorticoid resistance in acute lymphoblastic leukaemia (MLL)- AF4 (also known as KMT2A-AFF1) translocation.[32] Moreover this genetic alteration, dysregulated miRNA expression may rise from alteration in tumor suppressor or oncogenic factors, which functions as transcriptional activators or repressors to control pri-miRNA transcription. For example, effect of p53 on family of miRNA-34. The member of miRNA-34 family which promotes p53 activity also represses the growth promoting genes and commensurate with other p53 tumor suppressive factors to inhibit uncontrolled cell proliferation via apoptosis. In

cancer the protooncoprotein MYC activates the expression of oncogenic miRNAs along with miRNA-17-92 cluster.[33,34] The miRNA which targets MYC promote cancer activation by controlling the expression of E2F1, thrombospondin 1 (THBS1), connective tissue growth factor (CTCF) and other target mRNAs to regulate cell cycle progression and angiogenesis. The tumour suppressive miRNAs in B-cell lymphoma is repressed by MYC.[35] In addition the expression of miRNA 200 family is suppressed in multiple human tumors. In another addition, the cancer associated transcription factors like zinc-finger E-box-binding homeobox (ZEB1 and ZEB2), atypically regulate miRNA in many cancers. Therefore the main mechanism in cancer is the alteration of miRNAs expression via transcriptional dysregulation.[36]

3.1. Defective Microprocessor in cancer

The incipient pri-miRNA transcripts are generated by RNA pol II that forms a typical structure consisting of a stem-loop hairpin flanked by ssRNA. In nucleus microprocessor complex is present and microprocessor complex trims the pri-miRNA to generate pre-microRNA transcripts. Destabilization of DGCR8 mRNA is important to control the relative DGCR8 expression level which helps to maintain the homeostatic control of miRNA biogenesis in cell.[37-39] Dysregulation of this microprocessor complex often cause cancer. For example increased of copy number or over expression of DROSHA may cause advanced cervical squamous cell carcinomas.[40] It was reported that in multiple cancer DROSHA is highly expressed. Over expression of DROSHA alters the expression of miRNA and promotes cell proliferation, invasion, migration which facilitates to cancer progression.[40, 41] In many several type of cancer DROSHA expression level is downregulated. Downregulation of DROSHA results in low expression of miRNA which may cause metastasis, invasion[42] and reduced survival.[43-46] In lung, adeno carcinoma DROSHA is down-regulated resulting in cell proliferation and tumor growth in vitro and in vivo.[47] It was showed that DROSHA can function as tumor suppressor to inhibit the progression of cancer in many contexts. It was reported that in many cancer DROSHA is upregulated and in certain type of cancer DROSHA is downregulated, the mechanism is not well understood. So one possibility is that different cancers have different genetic or epigenetic mechanism, in this way the oncogenic or tumor suppressor miRNA is expressed abnormally in many types of cancer. In some cancer DROSHA is frequently mutated, like Wilms tumor samples.[48-51] More than 70% mutation of DROSHA occurs at E1147, it is a metal binding residue in the RNase IIIb domain. The somatic missense mutation of E1147K which makes it feasible to interact with metal binding and therefore the function of DROSHA is altered to process the pri-miRNA.[48-51] In ovarian cancer the missense mutations and a splice site mutation of DROSHA have been found. It was also reported that the expression level of DGCR8 is dysregulated in several cancers. In Wilms tumour mutation of DGCR8 were found, a frequent mutation (E518K) in dsRBD1 results in decreased expression of crucial miRNA in tumors.[49-51]

3.2. Pre-miRNA export in cancer

Pre-miRNA are exported from nucleus to cytoplasm by an nuclear export factor to be processed into mature miRNA. XPO5 and the cofactor RanGTP helps in this export of pre-miRNA. The XPO5- inactivating mutation may cause several tumors like sporadic colon, gastric and endometrial tumors. These XPO5 mutation results in weaken the export mechanism of XPO5 for that reason miRNA biogenesis is hampered.[52]

3.3. DICER1 mutation

Pre-miRNA is trimmed furtherby a protein complex including DICER1 and TRBP to form ~22 nucleotide long mature miRNAs.[53] DICER1 is a large multi-domain nuclease that contains two helicase domains, a dimerization domain, a PAZ domain, two RNaseIII domains and a dsRBD. DICER1 participates in the assembly of the minimal miRNAISC which helps in the function of miRNA to repress the target gene expression.[54] Reduced number of DICER1 promotes cell proliferation and tumorigenesis, which indicates the important role of DICER1 in oncogenesis.[47, 55] DICER1 mutations were first identified in pleuropulmonary blastoma (PPB), a rare form of lung tumour that is developed during fetal lung development.[56] Nonsense mutation or frameshift mutation affects DICER1 upstream of the region encoding RNaseIII domains, resulting in shortened DICER1 proteins which are lacking the C-terminal catalytic domains. These mutations mainly affect the RNase IIIb domain may results in defects in the function of RNase IIIb domain. The metal binding residues like E1705, D1709, G1809, D1810 and E1813 are mainly the mutation-prone zone.[57] The expression of let-7 tumor suppressive miRNA family is strongly reduced by mutation of DICER1 RNase IIIb. In cancer the DICER1 expression is often dysregulated. According to the type of the cancer the expression level of DROSHA and DICER1 may increased or decreased. DICER1 expression is targeted by many oncoproteins and tumour supressors which regulates the cancer progression. So overall we can say that both the genetic mutations or dysregulation of DICER1 can results in abnormal miRNA expression and tumorigenesis.

3.4. TRBP mutations

In normal cellular response TRBP is associated with the processing of miRNA which has a great impact on tumour suppression. So the loss of function of TRBP results in tumour formation. This lost function of TRBP is also related to dysregulation of miRNA. It is reported that two frameshift mutations of TRBP may lead to dysregulation of miRNA. These mutations actually reduced the TRBP and DICER1 expression which contributes to the defective processing of pre-miRNA. But in case of Ewing sarcoma family tumour (ESFT), the

reduced level of TRBP expression contributes to the dysregulation of miRNA which leads to tumour growth.[58, 59, 60] There are several functions that is operated by miRNA. miRNA binds mRNA via seed sequence which s hare identical sequence with the target mRNAs. Binding of miRNA and mRNA may results in the disstabilization or inhibition of target transcripts which is the reason of down regulation of respective mRNA encoded protein. These miRNAs have a huge impact in cancer. It is reported that the oncogenic miRNAs are often over expressed and tumor suppressor miRNAs are downregulated during the cancer, which may lead to change in the cell cycle.

4. Functions of miRNAs

4.1. MiRNAs involved in G1/S transition

It was reported that anti-proliferative miRNA-15a-16-1 cluster regulates cell cycle at the initiation stage. The two mature miRNA 15a and miRNA 16, expressed from the cluster, share the same seed sequence therefore they are from the same family. It is identified that miRNA 15a and miRNA 16 has a great impact in cancer. It is reported that this miRNA cluster is the target of some specific chromosome in case of chronic lympholytic leulemia (CLL) and others cancer and the activity of these miRNAs have been lost in about 70%.[61] At the G1 phase this miRNA-15a-16-1 cluster may induce cell cycle arrest by targeting critical cell cycle regulators such as CDK1, CDK2, CDK6 as well as cyclin (D1, D3, and E1).[62-65] Some other miRNAs can regulate these important cell cycle kinase complexes. Several miRNAs also target some positive regulators of CDK4/6 such as CDC25A, regulates CDK4/6 via phosphatase activity. Let 7, miRNA-15 family, miRNA-17, miRNA 19a, miRNA 20a and miRNA 34 are directly downregulated the levels of D-type cyclins. Cyclin D2 and E2 are directly downregulated by miRNA-26a.[66-73] Also miRNA-26a induces a G1 arrest of human liver cancer cells in vivo. Another miRNA-26a potentially inhibit proliferation of cancer cell and raise tumour specific apoptosis in vivo, for this reason there is a histrionic suppression of tumour progression without toxicity.[70] Cyclin E is reported to be downregulated by miRNA-16a and miRNA-34a.[74] Almost all of these miRNAs showed antiproliferative properties and they function as tumour suppressor. They remain inactive during Cancer. During hyper methylation tumour cells of different origins repress the synthesis of miRNA-124 and miRNA-137 thereby leading to CDK6 over expression. It has been seen that the over expression of CDK/cyclin complexes may results in amplified phosphorylation of retinoblastoma protein (pRB), which in turn activates E2F factors to drive G1 progression and S phase entry of cell.[75] Transcription factor of E2F family is important for cell cycle progression. Repression of the E2F activity is the key system by which the Rb family of pocket proteins assert its tumour suppressive functions. Cyclin dependent kinase (CDKs) phosphorylates for that reason they inactivates pocket proteins and allowing cell proliferation, which is controlled by CDK inhibitors. These E2F proteins are enabling to induce programmed cell death.[76] E2F1 factors induce some target genes which are responsible for apoptosis. This occurs mostly in the context of damaging of DNA results in E2F1 phosphorylation and activation which leads to apoptosis.[77, 78] MiRNA17-92 cluster and miRNA 17-5p and MiRNA-20a negatively regulates E2F1. More over in tumors samples from colon cancer patients the level of those miRNAs inversely proportional with E2F1 concentration, suggesting that these miRNAs promote malignancy in many tissues by rendering cells insensitive to the apoptotic abilities of E2F1.[79] In addition miRNA 17-92 cluster and other miRNAs also down regulates E2Fs. On the other hand E2F1 is inhibited by another miRNAs like 149, miRNA-330 and miRNA 331-3p, results in cell cycle arrest in prostate and gastric cancer cells.[80-82] E2F3 on the other hand is targeted by miRNA 125b, miRNA-210 and miRNA 195.[83-85] This property of E2F1 is shared by the tumour suppressor protein p53. p53 protein is a transcription factor and its increased expression leads to the induction of target genes that induce cell cycle arrest. In case of DNA damage, p53 is stabilized and phosphorylated and enhance the activation of p53 target genes.[76] E2F1 highly upregulates the levels of p53 and induces Tap73, homologue of a p53 having many functions of p53. p53 and E2F1 have positive impact on apoptosis. Most importantly the expression level of CDK inhibitor p21 is induced by the expression of p53, which active the Rb pocket via accumulation of hypophosphorylated that causes decrease in E2F1 activity (Ref). But there are also some reports on identification of miRNAs which are induced by E2F1 like miRNA 449. This miRNA, upregulates activity of p53 and induces apoptosis, shares seed sequences and target genes with the miRNA34 family. But this miRNA again reduces the activity of E2F1.[76] Overexpression of miRNA-106a downregulates pRB and interfere with CDK4/pRB. This event leads to facilitate cell cycle and the negative regulator of cell cycle entry and G1 progression.[86,87]

Some miRNAs tightly regulates some cell cycle inhibitors. MiRNA 24 and miRNA -31 controls p16, an inhibitor of CDK4/6.[88, 89] Both these miRNAs has an impact in regulation of proliferation and progression via regulating the expression of CDK inhibitor. P21, a target protein for p53, is a direct target of miRNA 17-92 cluster and miRNA 106b. $P27^{kip1}$ and $p57^{kip2}$ are controlled by miRNA 221/222 and miRNA 181. Abnormal expression of the miRNA 221-222 cluster is thought to activate CDK2 and enhance tumor growth by negatively regulation of both $p27^{kip1}$ and $p57^{kip2}$.[90] The overall mechanism demonstrated in Fig 2.

4.2. MiRNAs involved in G_2/M check point

While the G_1/S check point is the major one in which cells make a decision as to whether the cell cycle should progress, after DNA damages the cell cycle can also arrest at G_2/M. The G_2/M transition is activated by Cdc25 mediated dephosphorylation of the cyclin B/CDK

complex, also called mitosis promoting factor (MPF). Cdc25A also facilitates in G_1/S transition via activating cyclin D/CDK 4/6. Cdc25A dephosphorylates and activates complexes of CDK2 and cyclin A or E, which are responsible for initiation and progression through S phase. Phosphorylation leads to the rapid degradation of Cdc25A, resulting in cell cycle arrest in response to DNA damage.[91] In serum starvation, DNA damage and hypoxia miRNA 21 is induced. In colon cancer cells, miRNA 21 affects G_1/S and G_2/M transition by suppressing Cdc25A expression. Cdc25A also regulated by miRNA15A. High levels of miRNA-15A down regulate Cdc25A and inhibit cell proliferation and cytogenesis in polycystic disease. In contrast, low levels of miRNA-15A upregulates Cdc25A expression and promote cell proliferation and cystogenesis in normal rat cholangiocytes.[92]

4.3. Antiproliterative/Proapoptotic miRNAs

MicroRNAs with anti-proliferative and proapoptotic activity are likely to function as tumor suppressor genes. Hence they may not be expressed in cancer cell. One clear example is the family of let 7 miRNAs. The let 7family consist of a group of highly conserved miRNAs in multiple species. In human this regulation appears to be conserverd, where three RAS gene, known as potent oncogenes have also been demonstrated to be directly regulated by human let-7. In lung cancer RAS dysregulation is a key oncogenic event, loss of let-7 may contribute to pathogenesis in this disorder. Indeed, in cancerous tissue let-7 is generally expressed at low level compare to normal tissue and low expression of this miRNA correlate with shorter post-operative lung cancer survival. Expression of let-7 in lung cancer cell lines, directly suppress growth in vitro, further documenting the tumor suppressing activity of this miRNA.[93] It has been reported that miRNA 15-16 cluster has a pro-apoptotic property. It induces apoptosis by targeting the anti-apoptotic factor B-cell chronic lymphocytic leukaemia/lymphoma 2 (BCL2) at post-transcription level.[19,94] Like many other tumour suppressor, this miRNAs cluster is found to be frequently deleted in some B cell chronic lymphocytic leukaemia. In case of prostate carcinoma and pituitary adenoma the expression of miRNA 15- 16 is reduced, which leads to inhibition of apoptosis. Another miRNA-29b also shows similar function like miRNA-15-16. It was reported that in lung and prostate cancer the level of this miRNA is lost. It was also reported that in some other cancers the level of these miRNA is upregulated. For that reason, one contradictory examination that in these specific cancers these miRNAs may be deregulated other cellular process in accession to apoptosis.[19] The overall role of antiproliferative miRNAs are demonstrated in Fig 3.

4.4. Proproliferative/ Antiapoptotic miRNAs

Oncogenesis would likely promoted when some miRNAs show proproliferative and antiapoptotic activity and in cancer cell these miRNAs may be overexpressed. miRNA-17-92 cluster have these properties, it consists six miRNAs- miRNAs -17-5p,-18,-19a,-19b,-20 and -92. In human chromosome 13q31 this miRNA cluster is located, a place that is frequently evolved in several types of lymphoma and tumours.[95] In B cell lymphoma samples this miRNAs clusters are highly expressed.[96] It was reported that in lung cancer it has been recently observed that the number of these miRNAs is high (Hayashita et al, 2003). In lung cancer cell line, the entire miRNA cluster has been expressed but not individual one, which increases the cell proliferation. These discoveries suggest the oncogenic properties of these miRNAs cluster.[93] Another miRNA which show the antiapoptotic function is miRNA-21. It was reported that in glioblastoma tumour tissues this miRNA is highly expressed.[97] It was also observed that this miRNA is over expressed in breast cancer tissue.[98] This miRNA immediately targets phosphatase and tensin homologue (PTEN), results in the down regulation of PTEN which inhibits the protein kinase B (PKB), thus rate of the apoptosis is reduced in cancer cells. It was observed that miRNA-21 is overexpressed in case of hepato cellular carcinoma (HCC) and it targets proapoptotic factor programmed cell death 4 (PDCD4)[99], and frequently downregulates the expression of PDCD4.[100] It is also reported that miRNA-21 can avert apoptosis via inhibition of both PTEN and PDCD4. It was also reported that this miRNA play an important role in tumour invation and metastasis. It suppresses the tumour suppression genes like tropomysin 1 (TPM1)[101] and serin peptidase inhibition clade B (ovalobumin) member 5 (SERPINB5).[102] This miRNA-21 may upregulates multiple cancer associated pathways. The overall role of miRNAs are illustrated in Fig 4.

5. Impact of miRNA in cancers

Though several cancers are related with miRNA but we have chosen breast cancer, lung cancer and colorectal cancer for the discussion. The number of patients are suffering from these cancers are increased day by day. Thus it becomes very necessary to characterized the cancers in different ways to get more possible ways to resist it.

5.1. MiRNA and breast cancer

Breast cancer is common in women. Breast cancer starts when cells in the breast begin to grow out of control. Breast cancer is most primarily diagnosed cancer and lies one of the leading cause of cancer-related death in women worldwide.[103] Alterations of several signalling pathways, activation of oncogenic molecules, mutation in genes and non-targeted effect of chemotherapeutic effect which significantly contributes to the cancer progression. It was reported that miRNAs involved in tumour initiation regulating cancer stem cell (CSC) properties, including self-generating ability, tumourgenicity and durg resistance. Dysregulation of miRNAs leading to cause metastasis, escape from apotosis and tissue invation. In breast cancer several miRNAs have been identified as oncogenes and tumour suppressor and their functions have been characterized as

the regulators of tumour initiation, metastasis and Chemoresistance.[104]

Tumour initiation

It was reported that CSCs and cancer-initiating cells are mainly responsible for the tumour and cancer development. The properties of asymmetric cell division and ability to efflux small molecules are similar in both CSC and normal cell.[105] These differ from each other in tumour seeding and metastasis. In addition, the phenotypic plasticity of CSCs, i.e. the ability of these cells to differentiate into non-CSCs, is treated as an important factor for the prevention of tumour malignancy.[106] The first CSCs in solid tumours were identified and isolated from breast cancer. It was reported that high tumour-seeding ability have been seen in $CD44+/CD24^{-/low}$ Lineage-cells from breast specimens[107] and it was also reported that CSC properties such as self-renewal activity and tumour-seeding activity mainly regulated by let-7. $CD44^{+}/CD24^{-/low}$ antigenic phenotype is a key properties of CSCs and it can down-regulate let-7 expression significantly. It is also reported that let-7 inhibits the formation of breast cancer via direct targeting of the genes encoding RAS and high mobility group AT-hook 2 (HMGA2) which leads to inhibit the self-renewal and de-differentiation of cells.[104] The features of epithelial to mesenchymal transition (EMT) and high tumorigenicity was involved in metastasis and invasion of tumour cells. The characteristics of these cells are also $CD44+/CD24^{-/low}$. These cells population is also found in cancerous breast tissues. Loss of function of epithelial marker such as E-cadherin and the increasing the N-cadherin and vimentin, mesenchymal markers is characterized in EMT phenotype. Results in the loss of cell polarity, cell-cell adhesion and also allow cells to detach from each other and also achieve cell invasion capabilities. It was reported that in Madin Darby canine kidney cells undergoing EMT, miRNA-205, and five members of the miRNA-200 family namely miRNA-200a, miRNA-200b, miRNA-200c, miRNA-141 and miRNA-429 are selectively downregulated. Two members of miRNA-200 family, namely, miRNA-200a, miRNA-200b and miRNA-429 are located on human chromosome 1 and miRNA-200c, miRNA-141 on human chromosome 12. Upregulation of miRNA-200 inhibit the EMT phenotype, via increasing the transforming growth factor (TGFβ), tumour necrosis factor (TNFα) which mainly targets the genes encoding E-cadherin transcriptional repressors ZEB1 and ZEB2.[108] Function of these transcriptional repressors ZEB1 and ZEB2 increases the invasion and metastasis in human tumour. On another hand the miRNA-200c and miRNA-141 is also suppressed by ZEB1 which is a strong inducer of epithelial differentiation. So it may be concluded that the mutual interaction of ZEB1 and miRNA-200 family strongly regulate the EMT phenotype. It was also reported that miRNA 103/107 is also increase the EMT phenotype in breast cancer tissues. This miRNA-103/107 reduces the biosysnthesis of several miRNAs via targeting the genes encoding Dicer, leading to comprehensive down-regulation of miRNAs including miRNA-200 family which subsequently develop the metastasis and EMT phenotype in epithelial cancer cell.[109] B cell-specific Moloney murine leukemia virus integration site 1 (Bmi-1) is also target miRNA-128 and miRNA-200c resulting in the downregulation of these miRNAs. Loss of these miRNAs may up-regulated Bmi-1 in tumour cells.[110,111]

Resistance to drugs

Now-a-days a major problem with the cancerous cells is that they are resistant to chemotherapy and many molecular targeted drugs.[112] It was reported that the mechanism underlying drug resistance are mainly classified into two categories namely, the alteration of the structure of the drug transporters which efflux the anti-cancer agents[113, 114], and the activation of cell-survival and anti-apoptotic pathways.[115] In breast cancer several miRNAs have been identified that regulates the drug resistance property in many cancerous cells. High expression of ATP-binding cassette (ABC) transporter is the major cause of drug resistance.[116-118] Anti-cancer agents and some proteins are mainly effluxed out by ABC transporters.[112] ABC- transporter system associated with three transporters, namely, ABCB1, ABCG2 and ABCC1. There role in multidrug resistance connected with efflux of various hydrophobic compounds, including major anti-cancer agents such as taxanes, anthracyclines etc.[112, 119] The ABCC1 also known as MRP1, it is the first identified ABC-transporter, which is linked with the failure of chemotherapy treatment of various cancer, including breast, lung and colon cancer.[113,120,121] There are several miRNAs which is involved in regulating the ABC – transporte system. The expression of MRP1 is inversely related to the [miRNA-451.[103] The expression level of miRNA-451 is reduced in breast cancer. So the downregulation of miRNA-451 can also increased the level of MRP1 in breast cancer. The function of this transporter is to protect body from human environmental toxins. It functions to decrease the intracellular concentration of a broad spectrum antibiotics and durgs.[122] So, when it is highly expressed resulting in the drug resistance of cancer cells. For that reason miRNA-451 plays most important role, it regulates the expression of MRP1 and preventing the drug resistance. Another ABC- transporter ABCG2 also known as BCRP is also involved in chemoresistance in leukemia and breast cancer.[123,124] It was reported that several miRNAs like miRNA- 451 and miRNA- 326 are regulates the ABC-transporters like ABCC1 and increase the chemosensitivity.[122,125] Similarly the chemosensitivity of breast cancer cells also increase by the expression of miRNA-487 to mitoxantrane via targeting of ABCG2.[126] It was reported that several miRNAs are involved in another resistance mechanism of drug.[127,128, 129] Recent studies showed that the miRNA-221/222 is over expressed in breast cancer. Because $p27^{kip1}$ a cell cycle inhibitor and tumour suppressor is negatively regulates by miRNA-221/222.[129] It was reported that

another miRNA- 30c targets the actin-binding protein twinfilin1 which involves in EMT pathway that results in the suppression of the interleukin-11 and inhibits the resistance of breast cancers to paclitaxel and doxorubicin.[128]

Metastasis

Metastasis is a process that leading cause of the cancer death[130] therefore it is very much important to bring out the regulating mechanism of this process. At primary tumour site metastasis is arise.[131] Metastasis is caused by multiple complex processes resulting in cancer progression. It was reported that excessive vascularisation at primary tumour site was the main cause of metastasis. For that reason cell loss their property like loss of adhesion, achieve an invasion phenotype, allow cells to detach from each other and mobilization. In addition to Chemoresistance, miRNA are involved in modulating the metastasis process. The first identified miRNA was miRNA-10b in breast cancer metastasis. It was reported that miRNA-10b was first found higher in metastasis than non-metastasis breast cancer cell line. The expression levels of RAS homolog gene family member C is upregulates by the abnormal expression of miRNA-10b via direct targets the gene which encodes homeobox D 10 which may results in the promotion of invasion and metastasis.[132] It was also reported that some miRNA like miRNA-126, miRNA-206 and miRNA-335 is suppressed the breast cancer metastasis.[133] It have been identified that miRNA-126 reduces the cell proliferation and tumour growth. In another hand miRNA-206 and miRNA-335inhibits the metastasis. In breast cancer metastasis the miRNA-335 suppress the gene encoding the SOX4 transcription factor and the extracellular matrix component tenascin C. In addition it was also reported that in breast cancer metastasis the expression of miRNA-31 is downregulated. Another important factor that is multiple metastasis associated genes such as RhoA and ITGA5 (encoding integrin 5) is inhibited by miRNA-31.[134] During tumour invasion and metastasis one of the programmes is activated that is EMT. In another study it was again found that miRNA-34a, a transcriptional target of p53, repress EMT and Snail, a zinc finger transcriptional repressor[135] which may results in the inhibition of the invasiveness of breast cancer cells.[136] The EMT phenotype in breast cancer is also regulated by miRNA-22 and miRNA-200 family.[137,138] and these two miRNAs are an important factor that controls the initiation step of metastasis. The transcription factor GATA3 upregulates the miRNA-29b by suppressing the breast tumour metastasis.[139] MiRNA-29b also suppresses a network of pro-metastatic regulators which are associated with collagen remodelling, angiogenesis and proteolysis leads to inhibit the breast cancer metastasis.[139] It was also reported that cell migration and metastasis also regulated by miRNA-708.[140] These miRNAs is also targeting the endoplasmic reticulam protein neuronatin (NNAT), which regulates the intracellular Ca^{+2} levels. It was also reported that the phosphorylation of AGO2 at Tyr393 Position is a key factor of breast cancer progression.[141] The role of miRNAs in breast cancer is illustrated in Fig 5 and Table 1.

5.2. miRNAs and lung cancer

Lung cancer is one of the most common types of cancer and it is also the most common cause of cancer associated death in worldwide.[142] Lung cancer is known as lung carcinoma, and is characterised by the growth of uncontrolled cells in lung tissue. One of the process such as metastasis by which the growth can spread in the whole lung tissue and including other parts of the body. There are two types of lung carcinomas, small cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC).[143] SCLCs which metastasize earlier and are initially more sensitive to chemo than NSCLC, are mainly neuroendocrine tumors (NET). Adenocarcinoma (AD) and squamous cell carcinoma (SCC), are two main subgroups of NSLCS. Another third class of carcinomas separate of histological features of adeno and squamous differentiation, named large cell carcinoma (LCC).[143] In lung cancer several miRNAs also play an important role. Alterations of miRNAs can cause lung cancer. It was reported that miRNAs play an important role both oncogenesis and tumour suppressor.

Oncogenic miRNAs in lung cancers

The miRNA 17~92 cluster is act as an oncogenic miRNA and it stimulates the cancer progression. This miRNA is encoded by a gene located at 13q31.3 and is consist of six matures miRNA species- miRNA-17, miRNA-18a, miRNA-19a, miRNA-20a, miRNA-19b-1, and miRNA-92a 1.[144,145] The cluster of miRNA-17~92 was also named as oncomiRNA-1[146] exert the oncogenic behaviour in multiple types of cancer including- B-cell lymphoma, breast cancer, colon cancer, pancreatic cancer, glioblastoma, and retinoblastoma[147-152], etc. It was reported that in lung cancer, the cluster or this miRNAs are overexpressed resulting in the enhanced cell growth in lung cancer. One of the major marker of lung cancer is upregulation of miRNA-17~92 which is also known as “oncomiRNA addiction”. The inhibition of miRNA-20a and miRNA-17-5p with antisense oligonucleotides actually upregulates miRNA-17~92 that induces apoptosis.[153] MYC[154] and E2F[155] transactivate the expression of miRNA-17~92 and it is overexpressed in small cell lung cancers (SCLC).[156]

Another miRNA is miRNA-21, which is located on the chromosome 17 and it is one of the more studied oncomiRNA across the many cancer type. It was reported that miRNA-21 is upregulated in six types of solid tumour including lung cancer. It is an antiapoptotic factor. The miRNA-21 directly targets PTEN, a tumour suppressor gene. It was also reported that repression of the PTEN by miRNA-21 leading to enhance cell growth and invasion of NSCLC.[157] It is reported that RAS is upregulated in lung cancer. Further study demonstrated that miRNA-21 interact with the Spry1, negative

regulator of RAS. This miRNA also interact with others negative regulator of MEK, ERK pathway. This miRNA also targets important pro-apoptotic factors like Faslg, Apaf1, PDCD4 and RhoB. One of the study revealed that the targets of miRNA-21 involved in checkpoints of cell cycle. This research demonstrated the impact of miRNA-21on cell cycle regulation. The expression of miRNA-21 is repressed by FOXO3 and it increases the apoptosis in lung cancer.[158] Besides FOXO3 and RAS miRNA-21 also regulated by IL-6 in multiple myeloma cells.[159]

In recent studies it was found th at the new member of TNF family is the Apo2L/TNF-α-related apoptosis-inducing ligand (TRAIL) which induces the apoptosis in several cancers.[160] It was reported that the upregulation of miRNA-221/222 was seen in NSCLC cells which is resistance to TRAIL. The miRNA-221 and miRNA-222 are expressed from the same gene cluster located on X choromosome and they show the same seed sequence. This miRNA cluster mainly targets two genes kit and $p27^{Kip1}$. It was reported that in NSLCs cells, the levels of $p27^{Kip1}$ is decreased resulting in reduced sensitivity of TRAIL- induced apoptosis.[161] In another hand the miRNA-221/222 also targets two other factors PTEN/TIMP3[162] and PUMA[163] which may leads to the cancer cells TRAIL resistance. It was reported that in lung cancer upregulation of miRNA-221/222 is common and the functions of these miRNAs are involved in, activate the AKT pathway and metallopeptidase which may leads to the enhancement of the cancer progression.

There are some others miRNAs which also can promote the lung tumorigenesis. It was reported that miRNA- 494 is upregulated in many types of cancers, suggesting that it reduces the apoptosis in tumour cells via direct targeting the tumour suppressor PTEN.[164] One of the important tumour suppressing gene is FUS1 gene, in lung cancer the expression level of this gene frequently decreased.[165-167] It was reported that FUS1 is directly repressed by three miRNAs including- miRNA-98, miRNA-197, and miRNA-93. So downregulation of FUS1 may lead to promote lung cancer.[168] It was also reported that others miRNAs like miRNA-106, miRNA-150 are identified as oncomiRNA in lung cancer via targeting TP53 and RB respectively.[169]

Tumour suppressive miRNAs in cancer

The first identified miRNA was let-7 and also it was the first identified miRNA in human.[170, 171] They are tumour suppressive miRNA. In human there are 13 members of let-7 family was identified: let-7a-1, 7a-2, 7a-3, 7b, 7c, 7d, 7e, 7f-1, 7f-2, 7g, 7i, miRNA-98, and miRNA-202.[172] Another miRNA i.e. miRNA-34 which also act as a tumour suppressor. It was reported that this miRNA directly regulates the p53 network. It was found that miRNA-34a and miRNA-34b/c directly regulates p53 to control apoptosis and arrest cell-cycle in cancer cell lines.[173-176] Another miRNAs family identified later, miRNA-449a, miRNA-449b and miRNA-449c, together known as miRNA-449. They shared the same seed sequences and secondary structures with miRNA-34.[177] Thus, miRNA-34/449 family directly regulates p53 and E2F transcription factor. It was reported that miRNA-34 was activated by p53 and miRNA-449 was activated by E2F. E2F directly suppressed by both miRNAs but upregulation of p53 occured by targeting dyacetylase gene SIRT1. Researchers showed that in NSCLC samples miRNA-34b/c was significantly reduced but restoration of miRNA-34 negatively correlated with cell growth of lung cancer. In NSCLC miRNA-34 and miRNA-15/16 induced cell cycle arrest in RB dependent manner.[178] They directly targets the AXL[179] and SNAIL[180] were identified in lung cancer. It was also reported that in lung cancer expression of miRNA-449 a/b both are reduced. HDAC1 was realized as a target of miRNA-449a/b in lung cancer cells.[181] But the abnormal expression of miRNA-449a/b decreases the cell viability in lung cancer cell lines.

MiRNA-15a and miRNA-16-1 were identified which exert the tumour suppressor activity. In chronic lymphocytic leukemia (CLL) they are frequently downregulated.[182] The gene targets of this cluster includes: CDC2, CCND1, BCL-2, PDCD4 etc. By targeting these genes, this miRNA cluster actually regulates cell proliferation,survival and invasion.[93] It also reported that miRNA-15a and miRNA-16-1 also mutually with interacts with cell proliferation by targeting E2F1. Another report suggests that in NSCLC the over expression of miRNA-15/16 cluster may lead to decrease in the expression level of cyclin D1. The over expression of this cluster induced G1 aarrest which is a marker of lung cancer.

As we have discussed in breast cancer the miRNA-200 family and miRNA- 205 show similar role in case of lung cancer. The miRNA-200 family interact with miRNA-205 inhibited EMT via targeting both ZEB1 and ZEB2 transcription factor. It was reported that in lung cancer over expression of miRNA-200c reduces the ZEB1 expression. In lung cancer this miRNAs highly regulates the multi drug sensitivity[183] and also in multi drug resistance cells the expression of miRNA-200b/c and miRNA-429 were down regulated. The activation of drug-induced apoptosis is mediated by the inhibition of BCL-2 and XIAP, antiapoptotic factors. Another miRNA is miRNA-143/145 also act as a tumour suppressor. In lung cancer the expression of these miRNA is downregulated. MiRNA-145 targets EGFR, C-MYC, NUDT1 which may interact with proliferation regulation in lung cancers.[184-186] The function of this miRNA was regulates the cell cycle by G1 arrest targeting the CDK4 in lung cancer. MiRNA-145 targets OCT4, EGER and C-MYC factors and reduced the cell proliferation in lung cancer. Similarly miRNA-143 also regulates the lung cancer and the expression of this miRNA was also downregulated in chemical- induced mouse lung tumour. The role of microRNAs in lung cancer is summarized in Fig 6 and Ttable 2.

MiRNAs that exhibit both pro- and anti-lung cancer functions

It was also reported that some miRNAs exhibit both pro and anti- cancer activities in a context-dependent manner. The three miRNA-7 host genes located on chromosome 9, 15 and 19. It was reported that in glioblastomas it was act as tumour suppressor[187], directly targeting EGFR as well as downregulating AKT pathway to reduced invasiveness and viability in cancer cells. It was also reported that miRNA-7 inhibited A549 cell growth by targeting BCL-2.[188] On the other hand it was reported that miRNA-7 act as a oncomiRNA in lung cancers.[189] High level of miRNA-7 expression and significant correlation between EGFR and miRNA -7 expression in mutated EGFR but not in wild type EFGR in lung cancer. EGFR induced the miRNA-7 expression through the RAS/ERK/MYC pathway. Forced expression of miRNA-7 promoted tumorigenicity and proliferation of CL1-5 lung cancer cells by targeting Ets2 transcriptional repressor.[189] On the another hand miRNA-31 was located on chromosome 9 in human genome. The expression of miRNA-31 in lung can be induced by chemical carcinogens like vinyl carbamate and cigarette smoke.[190,191] Gain- and loss-of-function experiments established the role of miRNA-31 on enhancing proliferation and tumorigenicity of lung cancer cells.[191,192] MiRNA- 31 also target two tumour suppressor genes like LAST2 and PPP2R2A.[192] On the contrary miRNA-31 plays an tumour suppresors by targeting ITGA5 RDX, and RhoA[193,194], in breast cancer.

The another miRNA is miRNA-125 includes two members with identical seed sequences: miRNA-125a and miRNA-125b. Both miRNAs was identified as tumour suppressor as human breast cancer by targeting ERBB2 and ERBB3 genes and reduced their expression. Their tumour suppressor functions also found in other cancer like gastric cancer[195] and gliobastoma cancer.[196] But this miRNA-125a/b also acts as a oncomiRNA by targeting TP53 in lung cancer.[197,198] The roles of miRNAs in lung cancer formation demonstrated in Fig 6.

MiRNAs and Resistance

Chemotherapy in combination with radiotherapy was used in treatment against lung cancer, especially for NSCLC. The most common chemoresistance and radiation resistance achieved through long-term therapy. Now-a-days researchers frequently develop the new mechanism against resistance.

Resistance to Chemotherapy

In lung cancer the cells become Chemotherapy resistance. Some miRNAs play an important role for this resistant mechanism. One study reported that some miRNAs are involved to make the cell resistance to CDPP (cisplatin). Such as miRNA-503 make the cell resistance by targeting Bcl-2[199] and miRNA-136a/b by targeting MCL1[200], miRNA-31 by regulating the drug transporter ABCB9[201], and miRNA-15b by targeting phosphatidylethanolamine-binding protein 4 (PEBP4).[202] In certain tumour cells TRAIL can induced the apoptosis. It was reported that a significant proportion of human cancer cell resistant to TRAIL induced apoptosis. In human NSCLC cells are resistance to TRAIL. It was reported that miRNA-221 and miRNA-222 was found in TRAIL resistance in NSCLC cells compared to TRAIL sensitive cells. This miRNAs downregulates the TRAIL function by blocking the key regulatory protein, such as $p27^{kip1}$. Over expression of these two miRNAs can lead to invasive NSCLC tumour which is resistant to Chemotherapy.

Resistance to Radiotherapy

In tumour treatment the ionizing radiation (IR) plays an important role. It was reported that many cancerous cells have been resistance to this ionization resistance therapy but the mechanism of resistance is unclear. However some miRNAs play an important role in the modulation some key pathways which are involved in resistance mechanism. Activation of NF-κB1 is the primary criteria to make the cell IR resistance.[203] It was reported that the reduced expression of miRNA-9 and let-7 results in activation of NF-κB1 which leads to the resistant against radio activity.[204] On the other hand miRNA-214 is reported to be upregulated in radio resistance NSCLC cell lines. MiRNA-214 interferes with the activity of the caspase-3 and reduced its interaction with cells.[205] This event protects the cell from radio therapy induced apoptosis. Another study suggests that expression of miRNA-210 results in the radio resistance of normoxic cancer cell lines.[206]

5.3. MiRNA and Colon cancer

Colorectal Cancer(CRC), also known as colon cancer and bowel cancer, is the development of cancer from the colon. it is the third most common type of cancer. In past decades, it was observed that huge number of miRNAs expression has a functional role in the initiation and progression of CRC. It was reported that the expression levels of the miRNAs are globally reduced in cancer. In CRC miRNAs have more oncogenic than tumour suppressive.

In another study it was showed that miRNAs expression patterens are altered in CRC.[207] Over the last decades, studies have reported alternative factors like genetic mutations in tumour suppressor genes or oncogene may lead to change in the WNT pathway. Another reason of CRC development and progression is epigenetic variation including hypermethylation of various tumoue suppressor genes. This suggests that accumulation of genetic and epigenetic alterations may lead to colorectal cancer. It was reported that the expression levels of miRNA-143 and miRNA-145 is reduced in CRC, because these two miRNAs show tumour suppressive function. In another hand miRNA-342 also exerts tumour suppressive activity. Several miRNAs like let-7, miRNA-34, miRNA-342, miRNA-9, miRNA-129 and miRNA-137 all are tumour suppressive and are

hypermethylated in colon tumours and this is thought to lead to their reduced expression. For example, miRNA-143 directly targets DNA methyltranferase 3A (DNMT3A) and loss of miRNA-143 leads to increased DNMT3A in CRC cells. Similarly loss of miRNA-342 leads to increased DNA methyltranferase 1 (DNMT1) and this contributes to the hypermethylation of several tumour suppressor genes in CRC.[208]

Recently a study demonstrated that three members of miRNA-34 family were regulated by p53 in cell lines. Expression level of two members of miRNA-34 was reduced in NSCLC cells whereas re-establishment of miRNA-34 inhibited the growth of NSCLC cell. This miRNA-34 family showed the tumour suppressor activity. It was reported that fleeting expression of miRNA-34 in human colon cancer suppressed the cell proliferation completely via downregulation of E2F pathway and upregulation of p53 pathway. On the other hand SIRT1 is directly inhibited by miRNA-34a and also upregulates the levels of acetylated p53. As miRNA-34a suppressed the SIRT1 which is increase the apoptosis in wide- type of human colon cancer but not in human colon cancer lacking p53. So it suggested that p53 and miRNA-34a show positive feedback loop,and that it could act as a tumour suppressor through SIRT1-p53 pathway.[209,210]

One of the innate cytokine is macrophage migration inhibition factor (MIF) which is plays an important role in host control of immunity and inflammatory, which is also suppressed the p53 activity. In colorectal carcinogenesis MIF play an important role and MIF is potentially target of miRNA-451.[210] Several studies suggest that miRNA-451 reduced the cell proliferation in colorectal cancer because it was also show the tumour suppressive activity and also increased their susceptibility to radiotherapy.

Another miRNA that is miRNA-21 shows the oncogenic property, resulting in tumour initiation, progression and metastasis. Increased expression of miRNA-21 leads to the cell proliferation, decreased apoptosis, intravasation, cell migration and metastasis by targeting several tumour suppressor genes. Tumor suppressor genes experimentally-verified to be targeted by miRNA-21 include programmed cell death 4 (PDCD4)[211,212], phosphatase and tensin homolog (PTEN[213], Cell division cycle 25 homolog A (Cdc25a)[214], reversion-inducing-cysteine-rich protein with kazal motifs (RECK)[215], Maspin[216], nuclear factor 1 type(NFIB)[217], tropomyosin 1 (TPM1)[218], sprouty 2 (SPRY2)[219], T-lymphoma invasion and metastasis-inducing protein 1 (TIAM1)[220] and Ras homolog gene family, member B (RHOB).[221]

In CRC several other miRNAs have been implicated. One of the tumour suppressor miRNA like miRNA-30-5p directly targets denticleless homolog (DTL) to suppress tumour growth in CRC.[222] Tumour suppressor genes p53 is regulates by two miRNAs like miRNA-215 and miRNA-192 which may leads to suppress colon carcinogenesis.[223] Another miRNA-34a which is regulates the 53 can inhibit the cell invation in colon cancer cell lines by directly targetin the Fos-related antigen 1 [FRA1].[224] Another report suggests that miRNA-101 negatively regulates cyclooxygenase and this may contributes to initiation and progression of colon cancer.[207] MiRNA-449-5p targets FOXO4 and pro-apoptotic factor PDCD4 to promote cell invasion and migration in CRC cancer cell lines.[225] Another report suggested that tumour suppressor RB protein is inhibited by miRNA-675 that also increases the tumour growth.[226] Another report also suggests that miRNA-365 act as a tumour suppressor which reduced cell-cycle progression and induced apoptosis by targeting Bcl-2 and cyclin D1 (CCND1) in CRC cell lines.[227] One of the oncogenic miRNA is miRNA-95 repressed the expression of reporter gene coupled to the 3´- UTR region of sorting nexin 1(SNX1).[228] Moreover miRNA-95 inversely correlated with SNX1 proteins in human CRC tissue. Another factor MMP2 which help to promotes metastasis in CRC, also regulated by miRNA-29.[227] High expression of miRNA-29 may leads to inhibit the MMP2 protein, reduced colon carcinoma. Role of microRNAs in colorectal cancer is summarized in Fig 7 and Table 3.

Alteration of miRNAs contributes Chemoresistance

Chemoresistance to colorectal cancer is associated with 5-flurouracil (5FU).[230] MiRNA-21 is the main component which is involved in resistance to 5FU.[231] Over expression of miRNA-21 results in the downregulation of Muts homolog 2, a DNA repair protein. 5FU actually drives the cell towards the genotoxic stress. MiRNA-21 is mainly responsible for the combact this stress. In addition some results support thats alteration in the expression of miRNA-140, miRNA-224, miRNA-215, miRNA-20a are leads to develop chemoresistance.[207]

6. Therapy

Since miRNAs play important roles in the regulation of tumor initiation and development, modulation of miRNA activity is a promising approach for cancer treatment. Recent studies suggest that restore the function of tumour suppressor miRNAs by using expression vector or miRNA mimics and also inhibit the function of oncogenic miRNAs using expression vector containing complementary sequences or antisense oligonucleotides.[231,232] One of the important therapy is that MiRNA-based gene therapy provides an attractive anti-tumour approach for integrated cancer therapy. Approximately 3% of human genes encodes for miRNAs and upto 30% of human protein coding genes may be regulated by miRNAs.

6.1. Therapeutic approach to treatment breast cancer

Aromatic benzene-pyridine is used in miRNA based treatment for breast cancer. It inhibits nuclease

degradation of miRNA-205 and increase the stability of these miRNA.[233] 2'-O-methyl-4'-thiol also inhibits nuclease degradation of small RNAs. So, the modification of miRNA is a good approach for breast cancer treatment.[234] Using aptamers with specific receptor is a very promising approach for the treatment of breast cancer. This approach is used to suppress the tumourgenic activity of HMGA2 by applying conjugate-aptamer with let-7.

6.2. Therapeutic approach to treatment lung cancer

One of the best therapeutic approach for lung cancer is miRNA replacement therapy.[235] Repressing any miRNA by let-7 gives a promising response against lung cancer.[236] MiRNA-7 can also be inserted into the cell via liposome.[255] Another approach has been developed on the basis of miRNA-34a. Nano particle based delivary system become very effective for the treatment of lung cancer.[237] Like breast cancer like 2′-O methyl is also very effective for the treatment of lung cancer. 2′-O methyl inhibits the nuclease activity and stabilizes the miRNA.[238] AntimiRNA-150 is also very effective in lung cancer.[239] 8-mer locked nucleic acid [LNA] have been developed to inhibit the miRNA sharing identical seed sequences.[240] But still a huge amount of study needed in this field.

6.3. Therapeutic approach to treatment colorectal cancer

There are two miRNA based approaches are used for the treatment of colon cancer- restoring of tumour suppressor miRNA and inhibition of oncogenic miRNA. Antisence oligonucleotides have a great effect to inhibit the miRNAs. It is also reported that antimiRNA-122 can also be used to use as therapeutic agent for controlling colon cancer.

Research on miRNA based cancer treatment is established a promising way. Thus, miRNA based therapy has been developed for the treatment of cancer but still a huge amount of study needed in this field.[207]

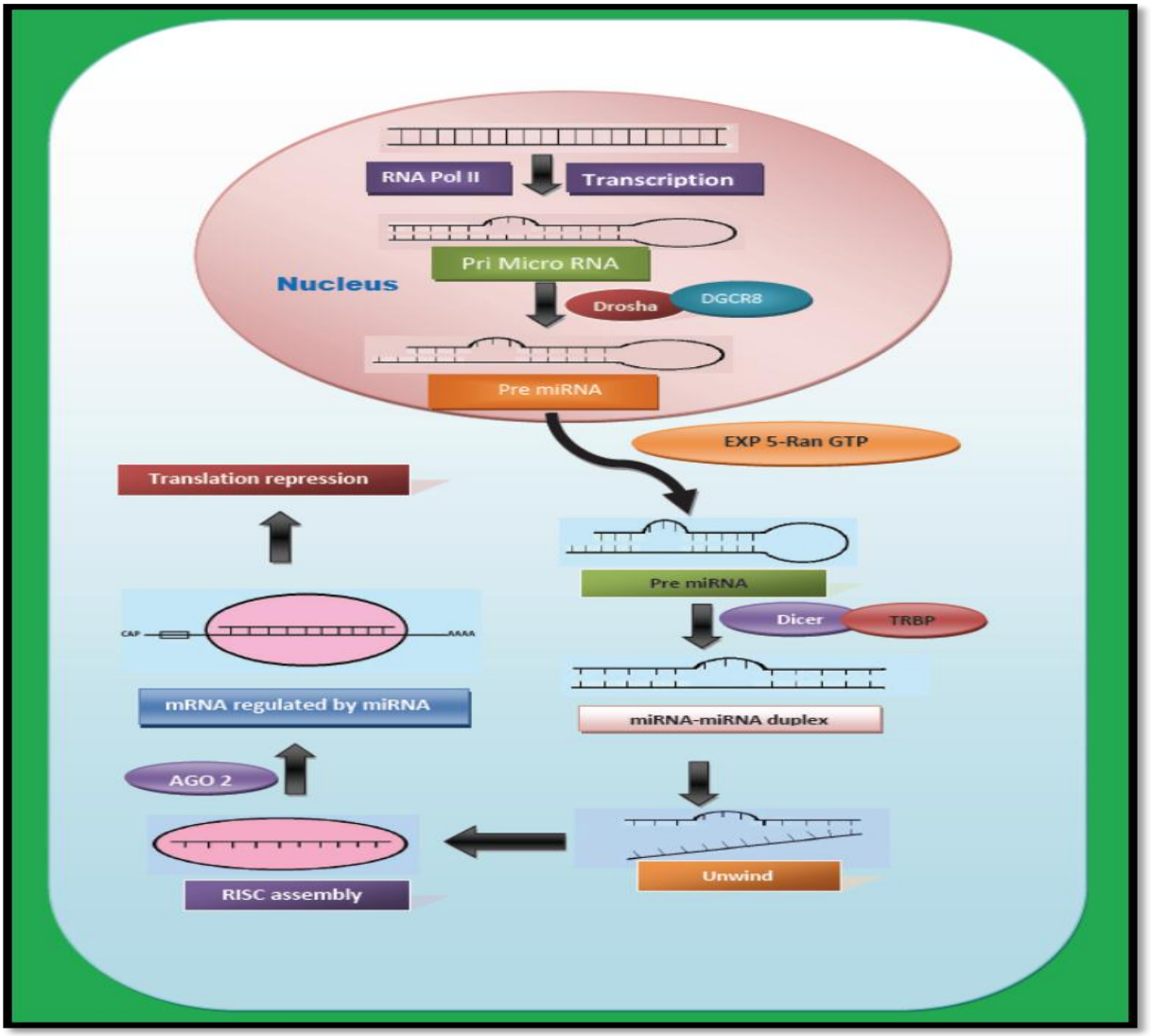

Fig1: Biogenesis of miRNA.

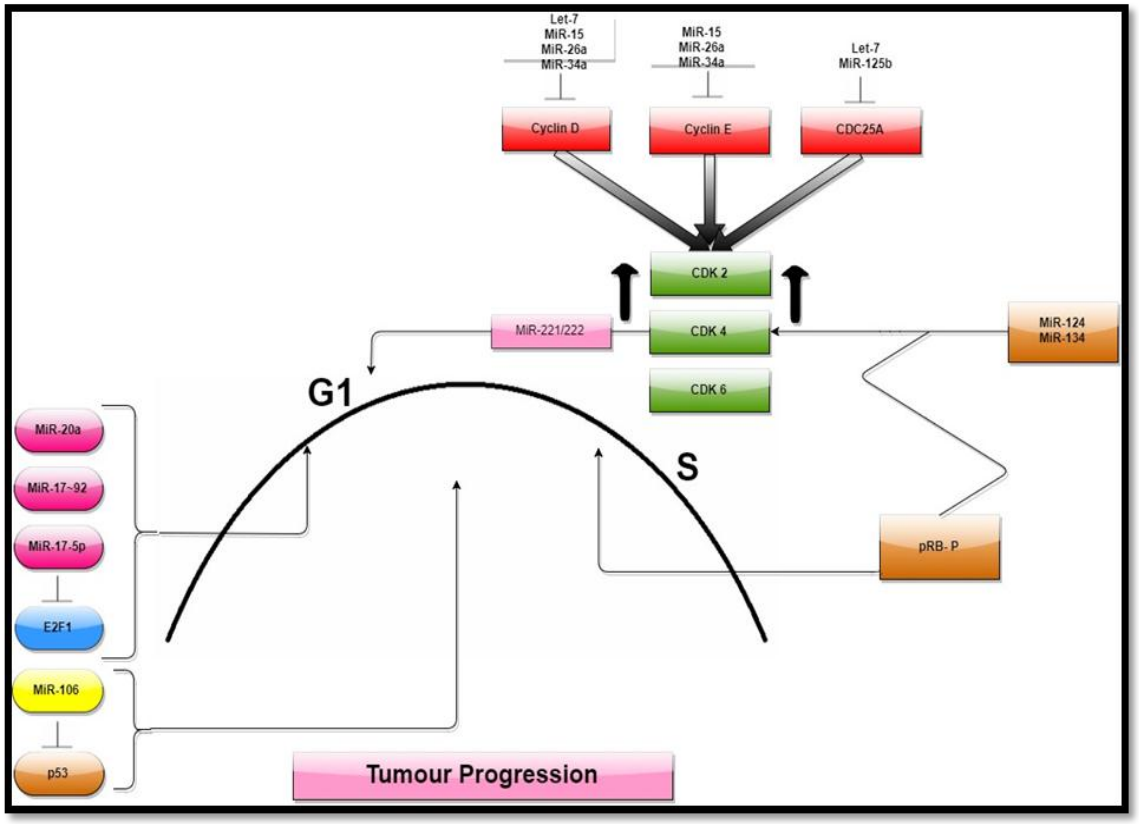

Fig 2: Change in the regulation of cell cycle via miRNAs in cancer cell.

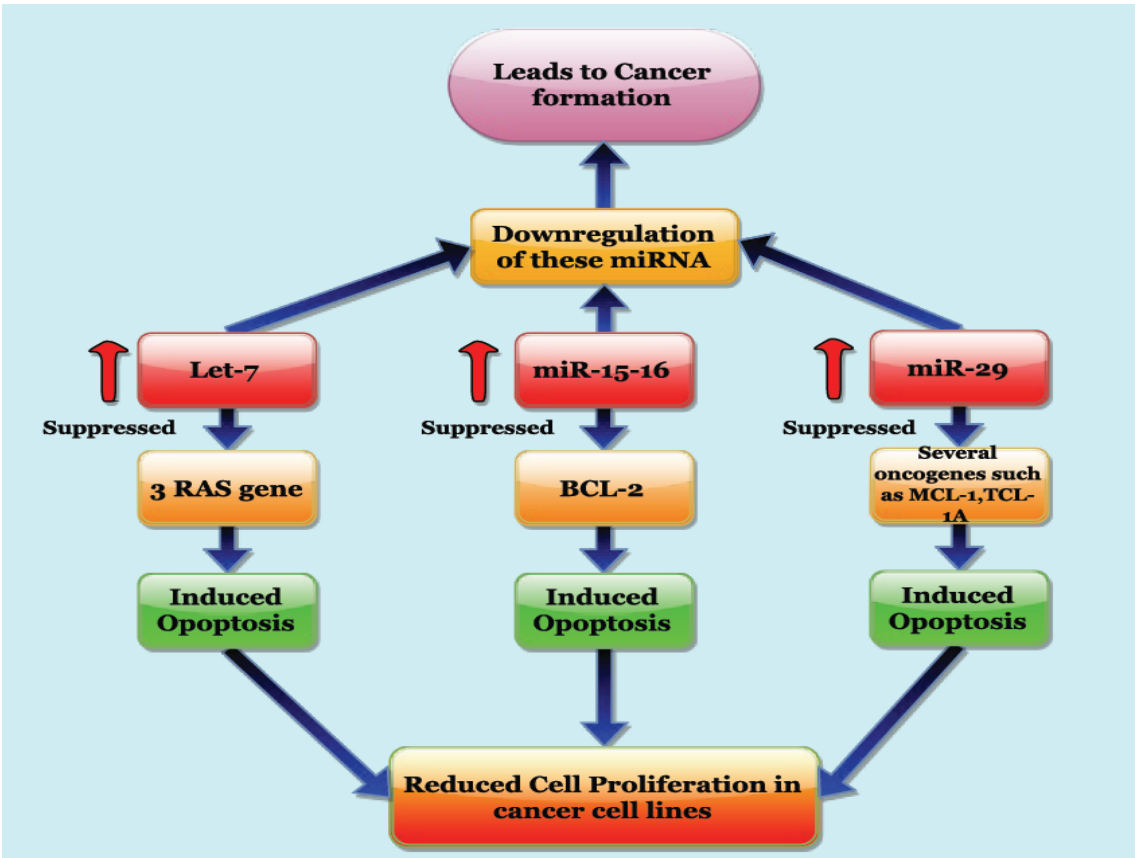

Fig 3: Change in expression of proapoptotic miRNAs that lead to cancer formation. Red arrow indicates upregulation.

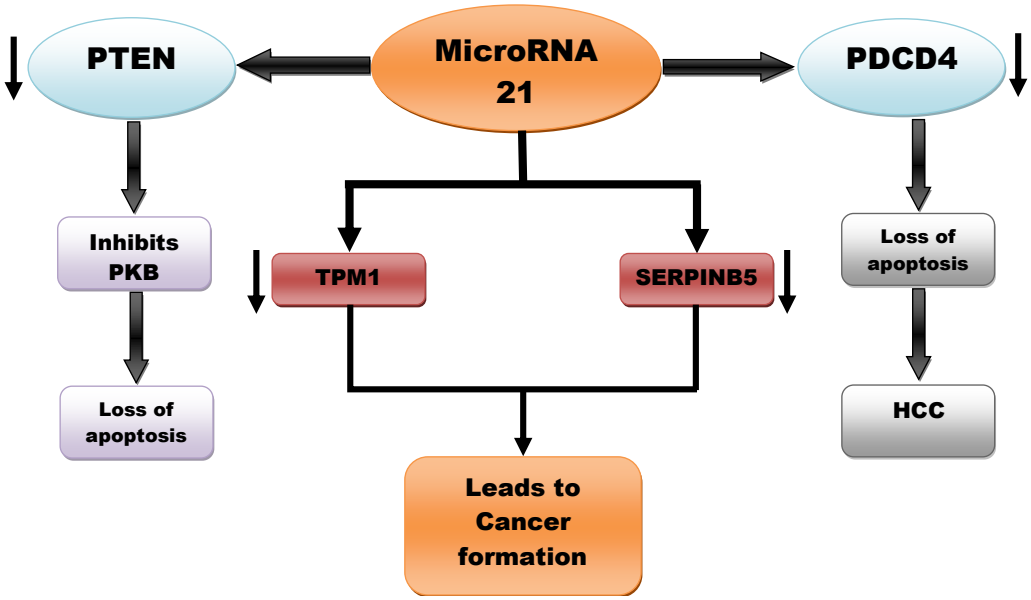

Fig 4: Change in expression of antiapoptotic miRNAs that lead to cancer formation. Black arrow indicates downregulation.

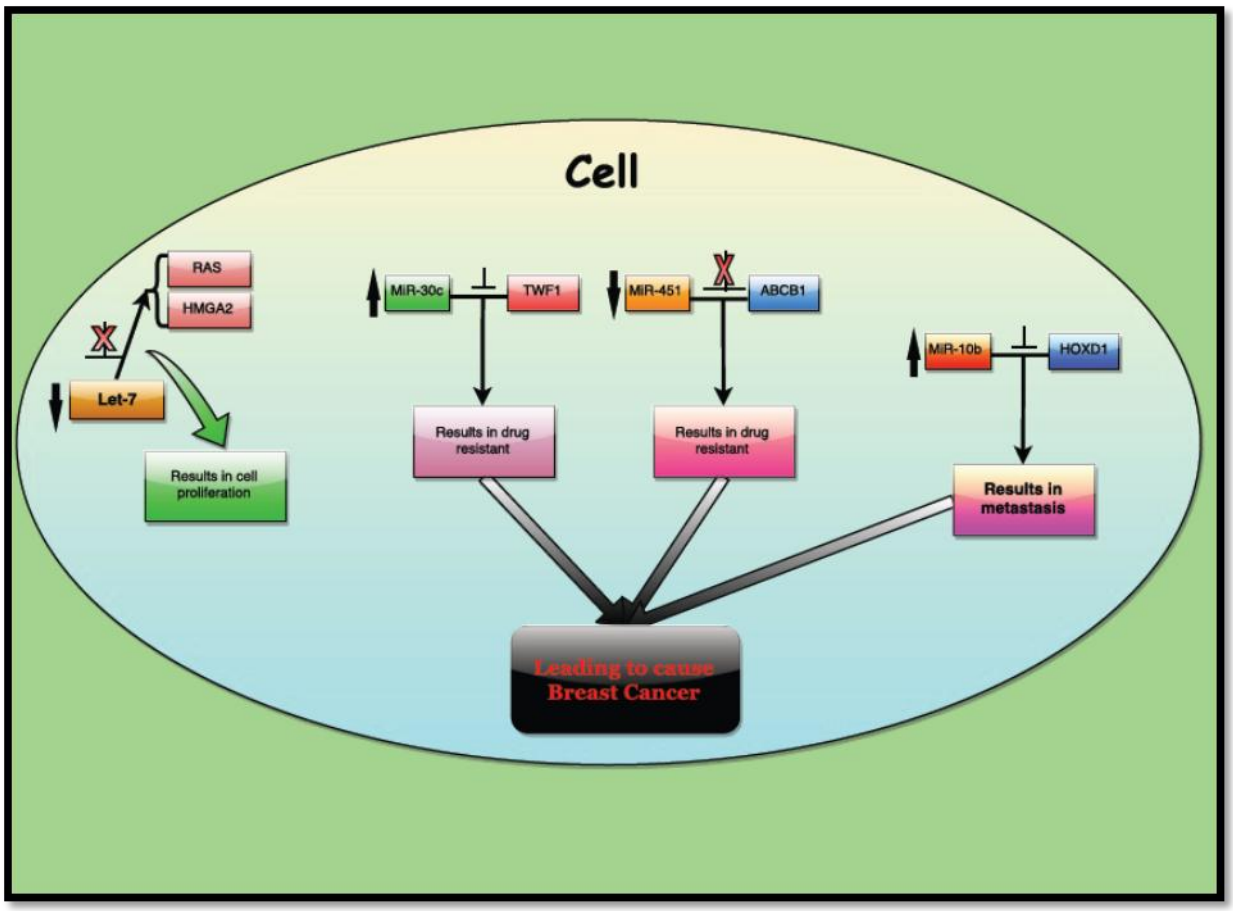

Fig 5: Role of miRNA in breast cancer. indicates upregulation, indicates down regulation.

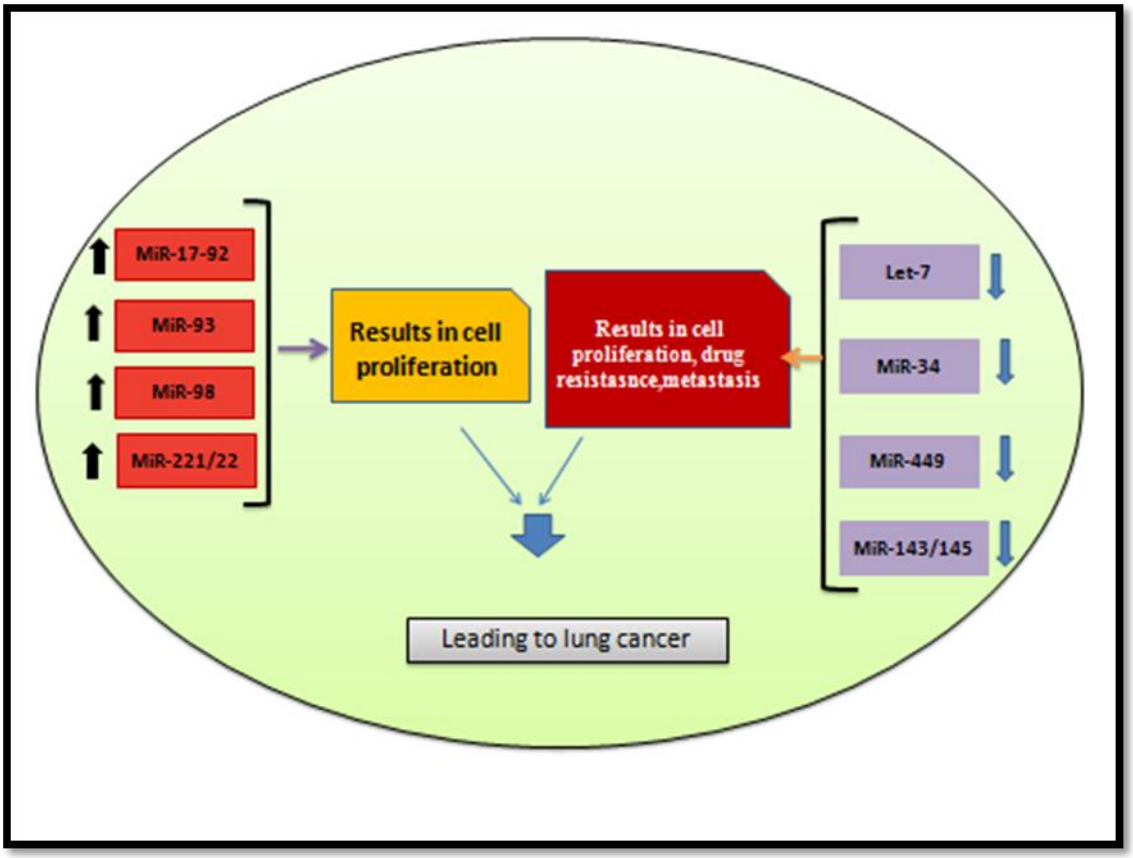

Fig 6: Role of miRNAs in lung cancer. Black arrow indicates upregulation. Blue arrow indicates downregulation.

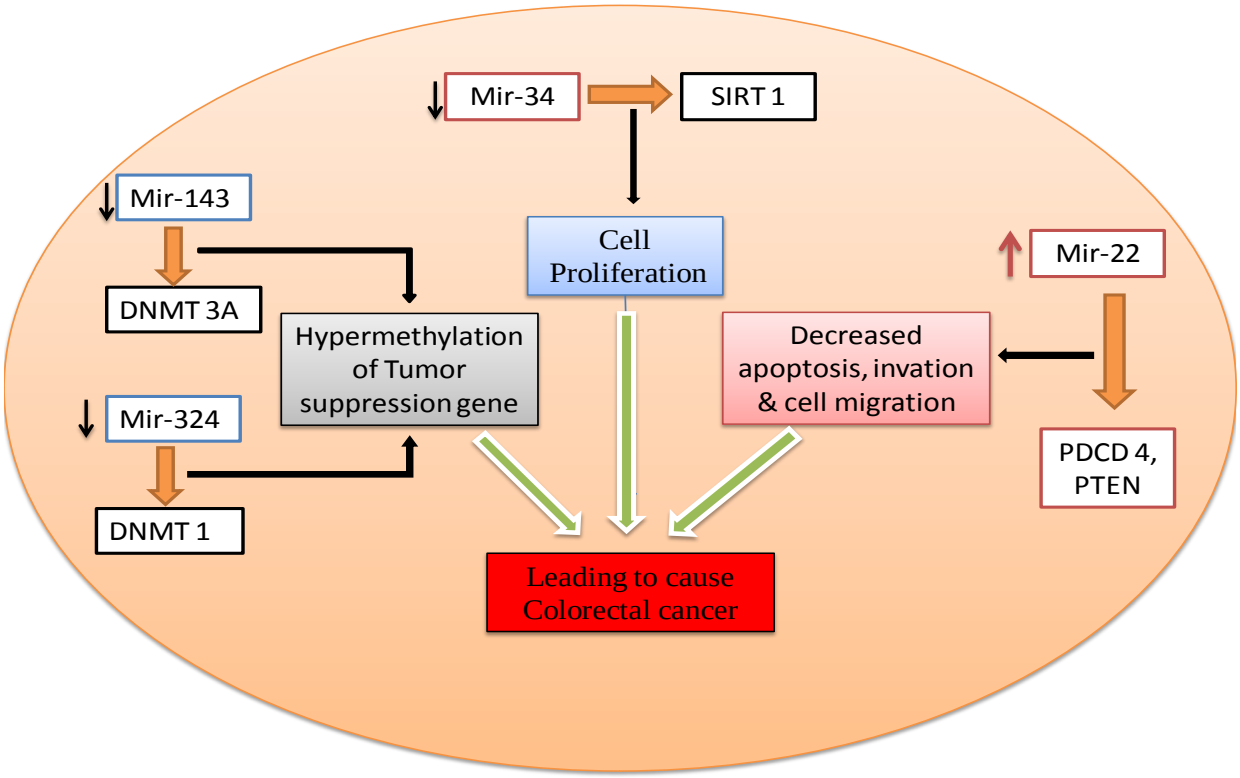

Fig 7: Roles of miRNAs in colorectal cancer. Black arrow indicates downregulation, Red arrows indicates upregulation.

Table 1: MicroRNAs are involved in Breast Cancer.

miRNAs genes	Phenotype	Target of	Upregulation	Downregulation	References
Let-7	TS	RAS, HMGA2		⬇	104
200-c	TS	BMI-1		⬇	110,111
MiR-200 family	TS	ZEB-1		⬇	108
MiR- 205	TS	ZEB-1,ZEB-2		⬇	108
MiR-103/107	OG	DICER		⬇	109
MiR-451	TS	ABCB1		⬇	103
MiR-326	TS	ABCC1		⬇	122,125
MiR-487	TS	ABCG2		⬇	123,124
MiR-221/222	OG	$p27^{kip1}$	⬆		129
MiR-30c	TS	TWF1 and IL-11	⬆		128
MiR-10b	OG	HOXD1	⬆		132
MiR-335	TS	SOX4, TNC		⬇	133
MiR-31	TS	RhoA & ITGA5		⬇	134
MiR-34a	TS	Sna il		⬇	135
Mir-29b	TS	VEGFA, ANGPTL4, LOX		⬇	139

[TS= Tumour suppressor, OG= Oncogene]

Abbreviations: ANGPTL4, angiopoietin-like 4; BMI-1, B cell-specific Moloney murine leukemia virus integration site 1; EMT, epithelial to mesenchymal transition; HOXD1, Homeobox D1; IL-11, interleukin-11; ITGA5, integrin 5_; LOX, lysyl oxidase; PKCepsilon, protein kinase C epsilon; TNC, tenascin C; TWF1, twinfilin 1; VEGFA, vascular endothelial growth factor A.

Table 2: MicroRNAs are involved in Lung Cancer.

miRNAs	Phenotype	Upregulation	Downregulation	References
MiR-17~92	OG	⬆		144
MiR-21	OG	⬆		157
MiR-221/222	OG	⬆		160
MiR-494	OG	⬆		164
MiR-98	OG	⬆		165-167
MiR-197	OG	⬆		168
MiR-93	OG	⬆		168
Let-7	TS		⬇	170,171
MiR-34	TS		⬇	173-176
MiR-449a/b	TS		⬇	177,180
MiR-200 family	TS		⬇	183
MiR-205	TS		⬇	183
MiR-143/145	TS		⬇	184-185

[TS= Tumour suppressor, OG= Oncogene]

Table 3: MicroRNAs are involved in Colorectal Cancer.

miRNAs	Phenotype	Upregulation	Downregulation	References
MiR-143/145	TS		⬇	207
MiR-342	TS		⬇	208
MiR-34	TS		⬇	209,210
MiR-129	TS		⬇	208
MiR-9	TS		⬇	208
MiR-137	TS		⬇	208
MiR-451	TS		⬇	210
MiR-21	OG	⬆		211,212
MiR-30-5p	TS		⬇	222
MiR-192	TS		⬇	223
MiR-215	TS		⬇	223
MiR-101	TS		⬇	207

MiR-675	OG	⬆		226
MiR-449-5p	OG	⬆		225
MiR-365	TS		⬇	227
MiR-95	OC	⬆		228
MiR-29	TS		⬇	227

[TS= Tumour suppressor, OG= Oncogene]

7. CONCLUSIONS

Change in the environment, pollution result in increase the rate of cancer. So it becomes very necessary to develop the treatment strategy for cancer. So keeping it is in mind we concentrated on miRNA as the marker of cancer. MiRNA will open a new possible way to counteract the lethal disease. Thus, in this review we summarized the role of miRNA in cancer. MicroRNAs are not only the regulators of many cancer related genes but also targets of many oncogenes or tumour suppressor gene such as RAS or TP53. So it becomes very important to characterize the role of microRNAs involve in different cancer. Here we discussed about the three cancers: breast cancer, lung cancer, colorectal cancer along with the therapies include chemo therapy, surgery, gene therapy and immune therapy. As we know dysregulation of miRNAs resulting in cancer formation and cells become chemo and radio therapy resistance. Because microRNAs can regulates several cancer related pathways. However RNA interference has huge therapeutic impact. So in contrast miRNA is believed to be relatively safe and has been more effective in cancer treatment. But several problems are also associated with this treatment approach. Thus, it becomes a topic of interest for oncologist.

8. ACKNOWLEDGEMENTS

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