JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

NON-CODING RNAs AND CANCERS

[1]Samawia Ifrahim, [2]Zill E Huma Akram, [3]Nimra Mazhar,
[4]Muhammad Faizan Tariq, [5]Muhammad Saad bin Tahir
[1]M.Phil Scholar [2]M.Phil Scholar [3]M.Phil Scholar [4]M.Phil Scholar [5]M.Phil Scholar

[1]Centre of Excellence in Molecular Biology University of the Punjab Lahore Pakistan

Abstract: Cancer has become a deadly disease in Pakistan. Cancer cells develop due to the mutations and elaborate changes in genetic makeup of the body. In this prevailing condition, control of cancer is crucial to help reduce the burden of this particular disease on different countries. Most common cancers diagnosed in Pakistan are breast, liver, colorectal, head, prostate, lung and neck, among which breast cancer is most widely spread in Pakistan**.** Conventional methods like chemotherapy and radiotherapy in Asian countries, including Pakistan are being practiced but now noncoding RNAs are being sought out for the treatment of this life-threatening disease. In Breast Cancer, micro-RNA-17-5p (miR-17-5p), miR-20a, 34a have been reported to reduce growth of cancerous cells which lead to breast carcinoma. MiR-34a-5p with targeted gene PD-L1 proved efficient in controlling lung cancer. In Liver cancer miR-121 and miR-203 are involved in tumor suppression. Roles of miR-205 and miR-34a are most widely studied microRNAs in prostate cancer. Moreover, 137 long noncoding RNAs (lncRNAs) were found involved in Chinese prostate cancer patients and being tissues. Oncogenic roles of miR-18a, -21, -31, and -92a as potential biomarkers for CRC have been observed in therapeutic treatment of colorectal cancer. Along with this, different researches have revealed the role of miR-194 as tumor suppressor by targeting Mitogen-activated protein kinase kinase kinase kinase 4 (MAP4K4). Studies have shown that Metastasis-associated lung adenocarcinoma transcript 1 (MALAT-1) is associated with tumor progression and metastasis. Thus, noncoding RNAs have proved efficient therapeutically but future studies are required which can help in combatting mortal disease like cancer.

IndexTerms **-** Cancer, miR-205, prostate cancer, tumor, noncoding RNA

I. INTRODUCTION

Cancer is a complex disease in which abnormal cells proliferate in uncontrolled way and sometimes metastasize to other cells. Cancer cells develop due to the mutations and elaborate changes in genetic makeup of the body. These changes include a cumulative group of gain-of-function mutations that trigger oncogenes, loss-of-function alterations that cause inactivation of tumor suppressor genes, and mutations that deactivate stability genes which are involved in unchecked cell division. All of these changes collectively help in the transformation of a cell to a malicious phenotype [1]. Moreover, other causes that lead to changes in genes include inherited genes, routine habits and sometimes being exposed to cancer- causing agents in environment thus causing uncontrolled growth of tumor cells. Tumor is lump or abnormal mass of cells that results due to unlimited and progressive cell division. A tumor which remains in original tissue and does not spread is benign tumor. Meanwhile some tumors are malignant that invades to other tissues and cells of the body. Tumors threaten the life of humans when their growth dislocates the tissues and organs that are needed for survival [2].

Cancer and its treatment can lead to severe complications such as weight loss, pain, tiredness, nausea, chemical changes in the body, brain and nervous system problems and rare immune responses to cancer [3]. Control of cancer is significant to help reduce the burden of this disease on countries and communities as millions of people die from cancer globally. Cancer control includes prevention of cancer, timely diagnosis and detection and effective treatment. Prevention of cancer is a step to reduce the risk of getting cancer. This may include avoiding exposure to cancer-causing substances, maintaining fit lifestyle and taking such drugs that can inhibit cancer development [4].

Cancer is the prominent cause of illness and death all over the world. The developing countries like Pakistan, Srilanka, Bangladesh which accounts for 75% of the world's population have reduced prevalence rates of cancer compared with the developed countries but tolerate more than half the worldwide cancer burden [5]. Asia being the largest continent in the world is the most affected. So, more than 48% of the cases with survival rate of less than 50%have been reported in Asian countries. As nowadays medical science has developed a lot but the mortality rate due to cancer is permanently increasing. It had been demanded that more than 9.5 million people lived all around the world with a death rate of above 50% in 2018 (GLOBOCAN, 2018). Cancer burdens the health management system and budget of a country, specifically an unindustrialized country like Pakistan [6]. The trends of disease aetiology should be monitored properly so that an effective prevention and treatment approach can be developed.

Most common cancers diagnosed in Pakistan are breast, liver, colorectal, head, prostate, lung and neck, among which breast cancer is most widely spread in Pakistan (Figure 1). Breast cancer will likely be gone on increasing if barriers are not removed for early screening and diagnosis. In Pakistan round 26,000 women were identified with breast cancer, and more than 13,500 women died of breast cancer in 2020 according to the World Health Organization (WHO). Pakistan does not have proper facilities for

treatment of cancer patients and according to different researches less than 40% of all cancer patients are able to have suitable care but many facilities are not available to more than 60% patients. Even the analgesic care, the treatment to dismiss symptoms caused by cancer is not available in Pakistan [7].

Although conventional treatments including chemotherapy, radiotherapy, and surgery are still available but oncological study is putting great effort towards investigating novel and proficient therapies which can help in alleviating serious side effects produced by conventional treatments. Moreover, targeted drug therapy, gene therapy, immunotherapy, nanomedicine are better approaches for cancer treatment [8].

Apart from these approaches, non-coding RNAs (ncRNAs) are recognized to contribute in several biological methods, control physiological and developmental procedures or even disease. Recently, non-coding RNAs have been elucidated as probable biomarkers that can notify diagnosis of cancer and early prediction by profound transcriptomics reporting of tissue and circulating non-coding RNAs in cancer patients. Clinical trials have also started for the investigation of non-coding RNA-based drugs as adjuncts to conventional chemotherapeutic drugs [9].

The length of ncRNAs is of few nucleotides to some thousands of nucleotides and it has been estimated that ncRNAs account for almost 98% of the human genome [10]. Generally, ncRNAs could be classified into two types: Classical housekeeping ncRNAs include transfer RNA (tRNA), ribosomal RNA (rRNA), small nucleolar RNA (snoRNA) and small nuclear RNA (snRNA). While regulatory ncRNAs include miRNA, small-interfering RNAs (siRNA), PIWI-interacting RNAs (piRNA), long non-coding RNA(lncRNA) and circular RNA (circRNA) etc. However, the role of miRNA and lncRNA has been explored more in literature [11]. This review summarizes the role of non-coding RNAs in cancer progression and also the potential role as therapeutic targets for cancer treatment.

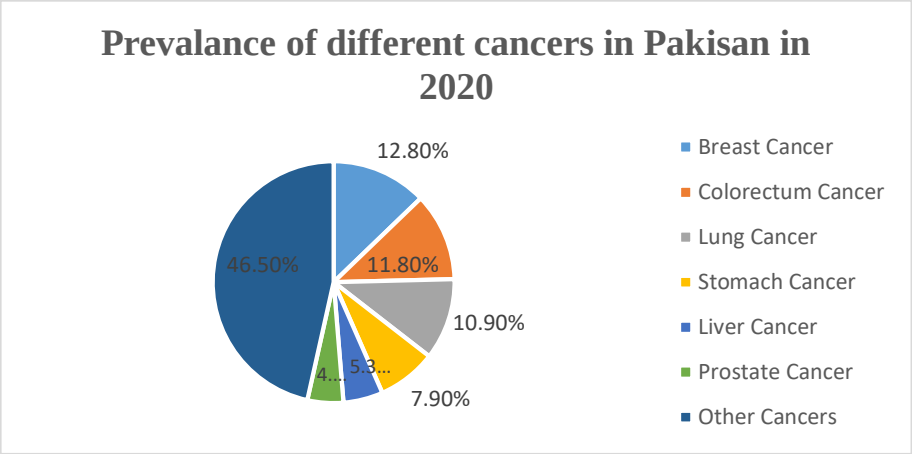

Figure 1: Prevalence of different types of cancers in Pakistan in the year, 2020

II. Role of Non-coding RNAs and Cancers

1. Non-coding RNAs in Breast Cancer

It is the most common cancer worldwide and as per global cancer statistics 2020, 2.3 million women got affected with the breast cancer [12]. Advanced treatment research focuses on non-coding RNAs that possess nice potential and will function potential prognostic and prognosticative biomarkers in breast carcinoma acting as promoters or inhibitors of carcinoma metastasis [13].

1.1 Role of miRNAs in Breast Cancer

Exosomal miRNAs, miR-17-5p and miR-20a target CCND1 (a molecule concerned in cell cycle). Expression of miR-17-5p and miR-20a area unit each downregulated in breast carcinoma, causes defect in Cyclin D1 synthesis and cell proliferation occurs [14]. p27Kip1, which expresses at high level once the cells aren't dividing, is associate degree substance of CDK1. Down-regulation of CDK1 p27Kip1 is very important for cells to manoeuvre into S-phase. miR-221 and miR-222 area unit up-regulated in breast carcinoma, that results in low levels of p27Kip1 and continuous cellular proliferation [15]. Anti-miRNA 2-O-methyl or secured supermolecule oligonucleotides won't inactivate oncomirs like miR-21 in breast neoplasms that could taper tumor growth [16].

Anti-miR-21–induced reduction in neoplasm growth is potentiated by the addition of the therapy agent topotecan, associate degree substance of desoxyribonucleic acid topoisomerase suggesting that suppression of the oncogenic miR-21 might sensitize neoplasm cells to metastatic tumor medical aid, that is associate degree exciting prospect for patients exhibiting a poor response to primary therapy [17]. Conversely, the induction of neoplasm suppressor miRNA expression victimization infectious agent or liposomal delivery of tissue-specific neoplasm suppressors to affected tissue could lead to the interference of progression or maybe shrinking of breast tumors [18].

The miRNAs will modify carcinoma drug sensitivity. Development of multi-drug resistance (MDR) is that the results of hyperbolic expression of ATP-binding container (ABC) transporters. Among these transporters, the multidrug-resistant macromolecule one (MRP1) is downregulated by miR-326 and controls neoplasm cell sensitivity to many therapy agents as well as antibiotic and etoposide. Of note, miR-326 has been found under expressed in an exceedingly panel of advanced breast cancer tissues [19]. miR-451 is reduced in doxorubicin-breast neoplastic cell lines compared with parental cells. Transfection of resistant cells with microRNA-451 hyperbolic cell sensitivity to antibiotic, indicating that manipulation of miRNAs levels could have important implications for therapeutic ways getting to overcome drug resistance[20].

1.2 Role of lncRNAs in Breast Cancer

lncRNA expression is regulated by each transcriptional and posttranscriptional factors throughout breast carcinoma metastasis [21]. lncRNA, CRALA, has been found to be related to a poor prognosis in breast carcinoma patients beneath a neoadjuvant therapy treatment regime. This lncRNA was conjointly found to be overexpressed in vitro in breast carcinoma cells that are immune to therapy [22]. lncRNA ARA has been concerned in multiple signal pathways concerned in breast carcinoma development, as well as mitogen-activated macromolecule enzyme (MAPK) and cell adhesion-related signal pathways, further as pathways control cell cycle progression [23].

2. Non-coding RNAs in Lung Cancer

Lung cancer is a very common and a leading cause of death from cancer accounting for 19.4% cancer demises according to WHO. Based on histological results lung cancer is classified into 2 subtypes and those are non-small cell lung cancer (NSCLC) and small cell lung carcinoma (SCLC). Eighty-five percent of all the cases of lung cancer are accounts for NSCLC and these classified into large cell carcinoma, adenocarcinoma and squamous cell carcinoma (Inamura, 2017).

Among different non-coding RNAs, miRNAs have been majorly linked to a variety of biological activities includes malignant lung cancer behaviours [24]. Following the discovery that miRNAs have a role in lung cancer, attention has shifted to other kind of non-coding RNA known as lncRNAs.

2.1 Role of miRNA in Lung Cancer

The miRNAs are tiny ncRNAs of around twenty-two nucleotides that play a role in post-transcriptional gene silencing. A great number of new research have looked into miRNA-based lung cancer treatment and approaches might be divided into three groups restoring tumor suppressed miRNAs, reversing drug resistance and directly blocking oncogenic miRNAs [25].

It has been studied that in lung adenocarcinoma, the protein, PD-L1is the target that has been linked to EGFR wild type status and increased mortality. Its expression is indicative of how patients respond to PD-L1 targeted treatment. PD-L1 is regulated by miR-34a-5p through *TP53*.Immunotherapy may include the use of miR-34a in association with radiotherapy [26] and it will help ultimately help to treat lung cancer.

In vivo, tumor suppressive miRNA-34a-5p and miRNA Let-7b-5p suppressed KRAS-activated tumor proliferation. miRNA Let-7a-5p as well as miRNA Let-7c-5p have been found to slow the growth of NSCLC in vivo. Synthetic miRNA-34a-5p proved efficient in suppressing the development of subcutaneous xenograft NSCLC whether administered by the tail vein or intratumorally [27].

In SCLC patients, it has been investigated that miR-450 downregulation was associated with a lower survival rate.miR-450 suppressed the multiplication, penetration, and development of H510A SCLC cells as xenografts inserted in immunocompromised mice [28].

This was also revealed that in vitro, alteration of miR-196a expression influenced NSCLC cellular proliferation, invasion, and migration. These findings imply that miR-196a may influence invasion and migration in partly by suppressing *HOXA5*(homeobox A5). By modulating cytoskeletal reorganization, *HOXA5* may work with p53 to limit lung cancer cell invasion [29].

2.2 Role of lncRNAs in Lung Cancer

The therapeutic importance of lncRNA in lung cancer therapy cannot be overstated and lncRNA has emerged as a major research issue [30].

Many components have a role in either preventing or accelerating DNA damage. A tumor suppressor that has been thoroughly explored, exerts critical functions in DNA damage is P53.To execute its anti-cancer action, the lncRNA MEG3 activates p53.Several distinct lncRNAs are linked to p53's downstream actions. Whenever DNA is disrupted, p53 activates the transcription of the lncRNA stress accelerated noncoding (DINO), As a result, the stress response following DNA damage may be controlled. Furthermore, in the absence of DNA damage, particular production of lncRNA-DINO stimulates the defective signalling pathway and causes cell cycle arrest [31].

The antisense oligonucleotides (ASO) targeting lncRNA may be a potential strategy for anticancer therapy. ASOs suppressed metastasis in lung cancer and tumor development by knocking down MALAT1 that is metastasis-associated [32].

In NSCLC, lncRNA growth arrest specific 5 (GAS5) was found to be a tumor suppressor and this is through modulating p21, p53 and E2F1 post-transcriptionally to promote NSCLC cell apoptosis and decrease tumor development [33].

Another lncRNA MIR503-HG also inhibited NSCLC growth by suppressing the expression of cyclin D1, despite the fact that the precise mechanism has not been identified. EMT can be reduced by tumor suppressor lncRNAs through decreasing metastasis and EMT induction and also by downregulating key inducers [34].

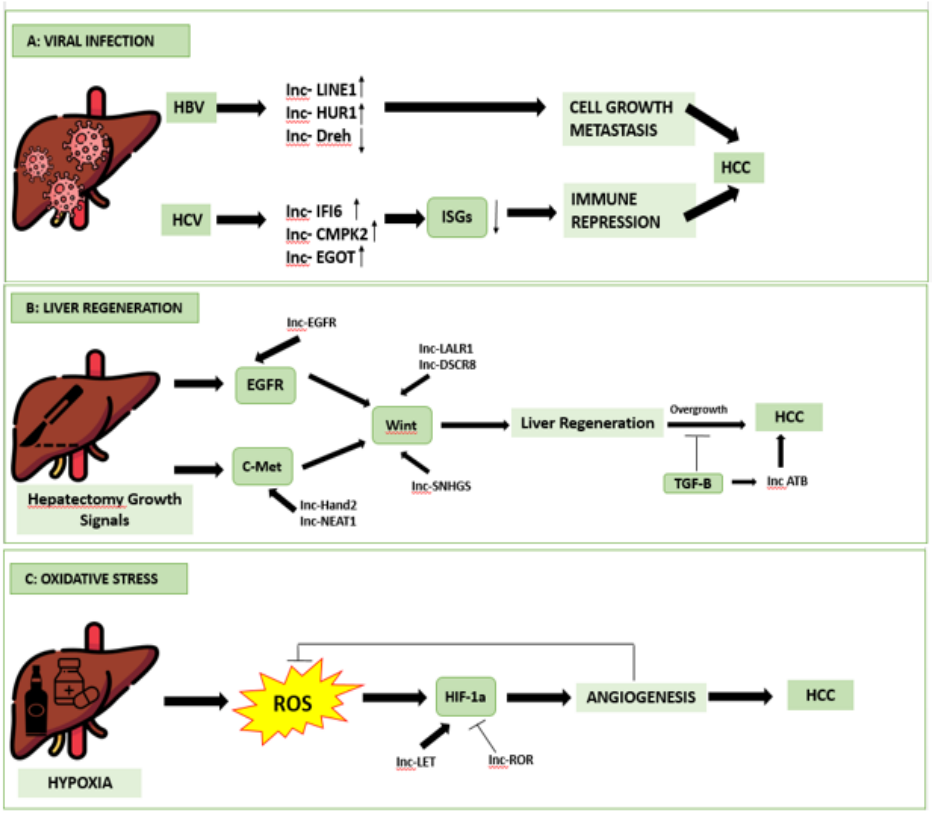

Figure 2: Role of various lncRNAs in liver cancer

3. Non-Coding RNAs in Liver Cancer

Liver Cancer or Hepatocellular carcinoma (HCC) is one of the most lethal and prevalent causes of death due to cancer, which causes deaths of 782,000 people every year [35]. Liver cancer is thought to be induced due to the progression ncRNAs through their multiple type of interactions with proteins, miRNAs or genetic variations. These interactions have influence on mechanisms like cell cycle, apoptosis, proliferation, invasion, and angiogenesis [36]. A large repertoire on non-coding RNAs such as lncRNA is now available.

3.1 Role of miRNAs in Liver Cancer

miRNAs perform the task of gene regulation post transcriptionally [37]. Mounting evidence suggest that in liver cancer, miRNAs are often deregulated, and variety of miRNAs are also found to be linked with clinopathological features of HCC [38].

Deregulated miRNAs have been reported to have role in a large pool of human disorders like cancer [39]. Two targets of miRNA-122 have been confirmed including Tumorigenesis Promotors like IGF-1 receptor and Serum response factor [40]. Role of miRNA in apoptosis has been validated, for example in Liver cancer, an apoptosis inhibitor, Surviving, is reported to be overexpressed and miRNA-203 is associated with controlling its expression [41].

In HCC, different studies by using miRNA-122 knockout mice models showed that, miRNA have been Downregulated. Liver inflammation, tumor development with age and fibrosis was observed in tested mice. The study also explored role of miR-122 as a tumor suppressor in liver and its functions.It is also reported that, chemically modified ssRNA “antagomirs”, complimentary to miRNA, were administered intravenously to inhibit expression of miR-122 [42].

3.2 Role of lncRNAs in Liver Cancer

LncRNAs are found to be associated with cellular differentiation, pluripotency, metastasis and proliferation [36]. For example, in the liver of mice, lncRNA H 19 is expressed during HCC and may induce drug resistance [43]. Due to advancement in techniques like High resolution microarray and MPSS, lncRNAs are thought to be important for oncogenesis, majorly in inducing HCC. Identified HCC related lncRNA dysregulations such as HULC, MALAT1, H19, Lnc-HUR1,Lnc-EGOT,LncNEAT,Lnc-ROR and HOTAIR have been reported (Figure 2).

An important lncRNA, MALAT1, has been observed to be associated with different solid tumors, cancer recurrence and metastasis. However, the role of MALT1 lncRNA is not well understood yet. In present study, expression of MALT1 was evaluated in 122 hepatocarcinoma patients and 9 liver cancer patients who had received Liver transplantation.

4. Noncoding RNAs in Prostate Cancer

Prostate cancer is a promising source of illness and mortality in men all over the world. It's the second most frequent cancer in males, next to the lung cancer, and the world's number five leading cause of death. [44].

4.1 Role of miRNAs in Prostate Cancer

Several researchers have investigated miRNA expression profiling in prostate cancer using a number of technologies. According to a common finding, miRNAs are specifically downregulated during prostate cancer growth and metastasis. Liu and associates [45] looked at miRNA expression in 6 prostate cancer stem/progenitor cell populations and discovered that a unique set

of miRNAs (downregulation of miR-34a, let-7b, miR-106a, and miR141, and upregulation of miR-301 and miR-452) operate together to restrict prostate malignant cells.

P53 regulates the miR-34 family, which has been involved in the negative regulation of cell cycle, senescence, and death [46]. The introduction of miR-34a antagomirs to CD44 prostate cancer cells increased tumor formation and metastasis, but forced expression of miR-34a prevented clonogenic expansion, tumor regeneration, and metastasis [47].This suggests that miR-34a inhibits the ability of prostate cancer stem cells to initiate tumors (Figure 3).

MiR-205 is perhaps the most studied tumor suppressor miRNA in prostate cancer. Hypermethylation of the MIR-205 locus is associated with a drop in miR205 expression in the prostate cancer cell line LNCaP (40-fold rise with 5-Aza-CdR treatment) and localized prostate cancer when compared to equivalent histologically normal prostate tissue. MIR-205 hypermethylation has also been discovered to be a powerful predictor of biochemical recurrence [48]. MiR-205 helps to prevent epithelial-to-mesenchymal transition (EMT) and limit cell migration and invasion by inhibiting EMT regulators ZEB1 and ZEB2, which suppress epithelial marker e-cadherin and upregulate mesenchymal marker vimentin [49].MiR-205 has been shown as a tumor suppressor by downregulating the EMT-related factors E2F1, protein kinase C, N-chimerin, and E2F5 (Figure 3).

4.2 Role of lncRNA in Prostate Cancer

PCGEM1 (prostate cancer gene expression marker 1) is a prostate-specific transcript found on the 2nd chromosome [50], was one of the first lncRNAs to be discovered in prostate cancer. In vitro, it increases cell proliferation and prevents apoptosis, albeit the molecular processes behind this are unknown. PCGEM1 is also thought to have a role in ethnic differences in prostate cancer incidence[51]. PCAT1 has been found to be elevated in a subset of metastatic and high-grade locally advanced malignancies, and to stimulate cell proliferation in vitro via influencing target genes via transcriptional control. [51].

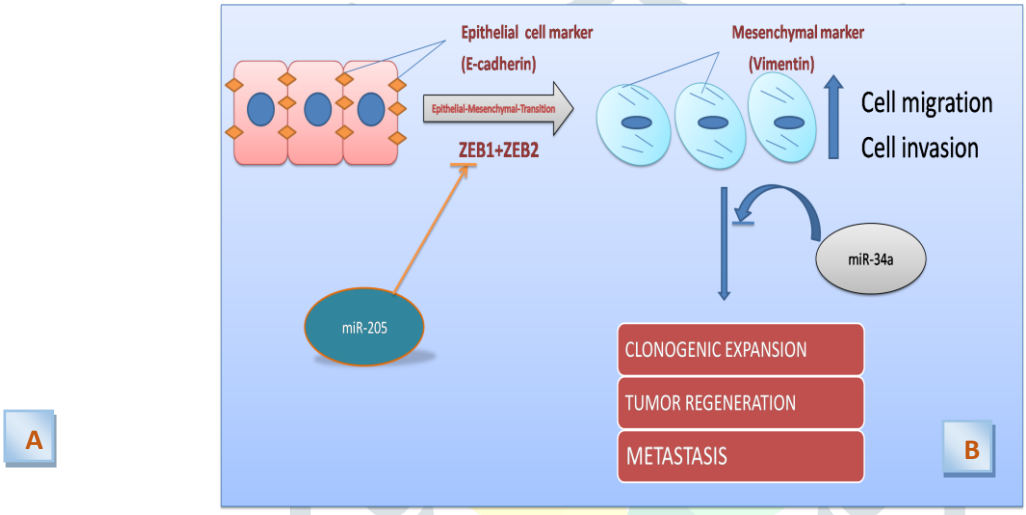

Figure 3: A diagrammatical presentation of miRNAs halting the prostatic clonal expansion. miR-205 inhibits the regulators (zeb1, zeb2) of EMT pathway (a). miR-34a inhibits the tumor initiation in prostatic stem cells (b).

Prostate cancer has also been linked to a number of other lncRNAs. 137 lncRNAs were substantially changed in 14 Chinese prostate cancers and surrounding benign tissues [52], according to a small RNA-Seq investigation. In malignancies, particularly prostate cancer, the CDKN2A–CDKN2B tumor suppressor locus is frequently deleted and hyper methylated. For tumor cells to survive and proliferate, telomerase activation and subsequent telomere maintenance are essential. The RNA component (TERC) of the telomerase core enzyme serves as a template for de novo telomeric DNA synthesis, while the protein catalytic subunit (TERT) operates as a reverse transcriptase. TERT is overexpressed in more than 90% of tumor cells, but TERC is found in all human tissues and is not affected by telomerase activity. Antisense oligonucleotide–mediated inhibition of TERC significantly reduced cell viability in PC3 and DU145 cell lines, as well as tumor formation in nude mice, via activating apoptosis [53]. Amplification of the TERC gene has been discovered in 5% of hormone mediated prostate cancers and almost 16% of CRPC malignancies. [54].

5. Non-coding RNAs in Colorectal Cancer

Being the third most malignant and second most preeminent basis of cancer mortality, colorectal cancer prevails throughout the world. The molecular mechanisms underlying the pathogenesis is mostly unrevealed, yet CRC progresses with the oncogene upregulation and downregulation of the tumor suppression gene resulting in epigenetic modifications consisting of non-coding RNAs and genetic mutations [55]. Non-coding RNAs can serve as a biomarker for cancer progression and potential therapeutic candidate for the CRC treatment [56].

5.1 Role of miRNAs in Colorectal Cancer

Many signaling pathways associated with the CRC progression determine the oncogenic or tumor suppressive role of miRNAs [56]. With oncogenic miRNAs associated in the development and progression of CRC, consisting of miR-18a, -21, -31, and -92a, serving as a potential biomarker for CRC, shown to play an oncogenic role in CRC partly through the downregulation of ATM and inhibiting the DNA repair [57]

Investigations about miR-194 clinical importance and biological significance in CRC has revealed that its downregulation has occurred in cell lines thus exhibiting the role of tumor suppression and inhibits cell progression and is associated with tumor activity and size. In addition, miR-194 has also seen to target MAP4K4 directly by regulating MDM2 expression transcriptionally. Thus, the results highlight the role of miR194 as tumor suppressor [56].

The altered expression of miRNAs is directly linked to the resistance of CRC to several chemotherapeutic drugs mainly the DNA replication interfering drug 5-fluorouracil and platinum-based drugs [58]. On the other hand, the tumor suppressive role of miRNAs has been seen to reverse the resistant behavior of CRC tumor to drugs by altering the expression of certain genes and making the CRC cell sensitive to drugs like oxaliplatin used in chemotherapy giving it the potential to be used as the target biomarker for treating CRC resistant to chemotherapy [59].

5.2 Role of lncRNAs in Colorectal Cancer

Another class of non-coding RNAs whose aberrant expression corresponds directly to the tumor progression in CRC are the long non-coding RNAs that server as a new diagnostic hallmark for colorectal cancer [60]. There is a diversity of mechanism through which lncRNAs either act as an oncogene or a tumor suppressive gene, by interacting with either DNA, RNA, or protein to form complexes for gene target [61].

MALAT-1 also known as the Metastasis-associated lung adenocarcinoma transcript 1 is a lncRNA with locus 11q13, is highly involved in metastatic cancer and increased expression in CRC progressive tumors [62]. Studies have shown that MALAT-1 is associated with cellular migration, proliferation and invasion of CRC tumor promoting its metastasis [60, 63].

HOX transcript antisense intergenic RNA or HOTAIR is a lncRNA with the locus 12q13.13, whose upregulation is closely related to the progression of CRC and is shown to directly involve in cell invasion and migration by stimulating chromatin changes mainly by modifying histone proteins [64]. Similarly, the modification in the level of lncRNA expression by various epigenetic, transcriptional, genetic, and regulatory factors controls the malignancy of tumor progression [65].

However, the differential regulation of lncRNAs may serve as a potential for therapeutic CRC targets as they are involved in modulation of tumors as oncogenes. The introduction of RNA interfering mechanism of siRNA against specific lncRNA such as HOTAIR have promising anticancer attributes [66]. The blocking of onco-lncRNA has been seen in mouse xenografted modals which showed reduction in both tumor volume and weight due to the over expression of tumor suppressive LOC285194 gene [67]. The use of gene therapy in manipulating lncRNA offers therapeutic role by designing personalized medicine and overcoming the barrier of drug resistance [68].Various miRNAs , their targeted genes and related pathways in different cancers are summarized in Table 1.

Table 1: Summary of miRNAs, their targeted genes/proteins and associated pathways in various cancers

MicroRNA	Target genes/Proteins	Associated Pathways	References
miR-17-5p, miR-20a, 34a	CCND1	DNA damage, proliferation	[14]
miR-221, miR-222	CDK1 p27Kip1	Tamoxifen resistance	[15]
miR-326	MRP1	ErbB/PI3K signaling pathway	[19]
miR-451	CCND2	Suppressor of angiogenesis	[20]
miR-21	*PTEN*	Oncogene	[57]
miR-18a	TBPL1	tumor suppression by P53 expression modulation	[57]
miR-192	MDM2 expression	Tumor suppressor.	[58]
miR-122	IGF-1, serum response factor	Tumor suppressor	[42]
miR-203	Surviving (apoptosis inhibitor)	Controls expression	[47]
miR-205	E2F1, E2F5, ZEB2 and Protein Kinase C	Tumor suppression by halting the epithelial to mesenchymal transition (EMT) regulation	[48,49]
miR-34a	CD44 knockdown	Prevent clonogenic expansion and metastasis of prostatic Stem Cells	[46,47]
CDKN2A, CDKN2B	CDK4 and CDK6	Control the entry of cells into S-phase	[53]

III. CONCLUSION

There are limited treatment options available for curing different cancers efficiently. Therefore, specific and sensitive prognostic, tumorigenic, and therapeutic targets are required crucially for the prevention and treatment of cancers. Insufficient knowledge of molecular biomarkers leads to full malignant tumor progression with the treatment option of surgery and traditional chemotherapy, there is a call for therapeutic biomarkers to treat different cancers. Non-coding RNAs proves to have an efficient therapeutic role and each new ncRNA discovery adds a new and sometimes surprising, layer to biological regulation and function these days. However, more research is needed to determine the significance of distinguishing the free circulating and bound ncRNAs in suppression and progression of various cancers the clinical application of ncRNAs in different cancers is still being explored in vitro and in animal models, and more study in these areas is required before their full potential can be explored.

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