*Int.J.Curr.Res.Aca.Rev.2021; 9(09): 7-18*

EXCELLENT PUBLISHERS

# International Journal of Current Research and Academic Review

**ISSN: 2347-3215 (Online) Volume 9 Number 09 (September-2021)**

Journal homepage: http://www.ijcrar.com

**doi:** https://doi.org/10.20546/ijcrar.2021.909.002

# Cancer Stem Cells: It's Future Perspective by Defining its Radiation Sensitivity and Resistivity through Differentially Regulated Expression of Micro-RNAs

**Suranjana Haldar[1*] and Atish Haldar[2*]**

[1]*Department of Zoology, State Aided College Teacher, Sarojini Naidu College for Women, West Bengal, India*
[2]*Purulia Medical College and Hospital, West Bengal, India*

**Corresponding author*

## Abstract

Stem cells are undifferentiated cells in the body that can self-renew, propagate differentiated cells, and proliferate extensively. They have the capacity and renewing themselves for indefinite periods. The consensus definition of a cancer stem cell arrived as a cell within a tumor that possesses the capacity to self-renew and to cause the heterogeneous lineages of cancer cells that comprise the tumor. The classical model of cancer formation, termed the stochastic model, defines tumor cells as biologically equivalent. Intrinsic factors, such as signaling pathways, levels of transcription factors, and extrinsic factors, result in varied and unpredictable behavior of the tumor cells. Conversely, the hierarchy model proposes that tumors are made up of biologically distinct types of cells with varying functions and behaviors. Tumor growth can only be initiated by a subset of cells known as cancer stem cells (CSCs). CSCs have a set of markers for detection and determination. Surface markers such as ESA, CD44+, are characterized in breast, ovarian, colon, prostate, pancreas or in head and neck cancer tissues while low CD24-, CD 45- found in breast or hepatocellular carcinomas. Micro RNAs (miRNAs) are involved in cancer pathogenesis by posttranscriptional regulation of gene expression. Specific miRNAs play a unique and important regulation role in characteristics of cancer stem cells. In further to find out full nature of the involvement of BCSCs in the molecular mechanisms of tumorigenesis or involvement of micro-RNAs (miRNAs) in the function of BCSCs microarray profiling of miRNAs of both ESA+CD44+CD24-low breast cancer stem cells and MCF7 cell lines were done (45). miRNA expression profiles of BCSCs and MCF-7 cells using a normalisation factor and clustering, identified differentially expressed 19 miRNAs that fell into two groups (fold change ≥ 4). Moreover, miR-301, miR-296, miR-21 and miR-373* have been reported to be expressed in human embryonic stem cells and other stem cells, indicating that these miRNAs may play a constitutive role in maintaining the biological characteristics of stem cells. A detailed understanding of miRNA mechanisms may also permit targeted therapeutic strategies based on miRNA inhibition or supplementation. The present review discuss all about the aspects of cancer stem cells and its identification through different surface markers and differentially expressed micro RNAs. The role of micro RNA up/down regulation is described in brief in this review with aim to take initiative for future onco-genomic research in implication of micro-RNA mediated CSC propagation in tumor metastasis.

## Article Info

*Accepted: 15 August 2021*
*Available Online: 20 September 2021*

## Keywords

Cancer Stem Cell, MiRNA, surface markers, growth factors, lung carcinoma, breast carcinoma, hepatic cancer.

## Introduction

## The Story behind Cancer Stem Cells

## Normal/ Cancer stem Cells

Normal stem cells are undifferentiated cells in the body that can self-renew, propagate differentiated cells, and proliferate extensively. Laboratory studies have shown that entire organs can be generated from a single stem cell (1). These discoveries have fueled interest in stem cell therapy for a wide variety of diseases, including neurological, inflammatory, and endocrine disorders (1). Cancer Stem Cells (CSCs) are malignant cancer cells that share the capacity of normal stem cells for self-renewal and proliferation and can differentiate into the heterogeneous population of cancer cells that comprise a malignant tumor (2).

The consensus definition of a cancer stem cell arrived as a cell within a tumor that possesses the capacity to self-renew and to cause the heterogeneous lineages of cancer cells that comprise the tumor. Cancer stem cells can thus only be defined experimentally by their ability to recapitulate the generation of a continuously growing tumor. The implementation of this approach explains the use of alternative terms in the literature, such as ‘‘tumor initiating cell’’ and ‘‘tumorigenic cell’’ to describe putative cancer stem cells.

## Clarifying the Concepts and Definitions

The term cancer stem cell has led to some confusion. A common misconception is that all CSCs arise from mutated normal stem cells, but some CSCs may arise from progenitor cells when a mutation endows these cells with the capacity for self-renewal, normally reserved to stem cells (3, 4). For example, in blast crisis chronic myelogenous leukemia (CML), a committed granulocyte-macrophage progenitor may acquire self-renewal capacity and thus ‘‘reacquire’’ stem-like properties due to the effects of later mutations. It is conceivable that more differentiated cells can, through multiple mutagenic events, acquire the self-renewal capacity and immortality that typify cancer stem cells. In both of these examples, a differentiated cell, not the tissue stem cell, eventually evolves to become a full blown cancer stem cell. The term tumor-initiating cell can also cause confusion. In some of the seminal studies in this field, the term ‘‘cancer initiating’’ has been used to refer to the ability of these cells to initiate tumors when transplanted. The tumor-initiating cell is often used to mean the cell that causes a tumor (or leukemia) in xenograft models of human cancer. Some have extrapolated that the cell that initiates a tumor xenograft is the same as the cell that received the first oncogenic ‘‘hits’’ in the patient. It is clear that the cancer stem cell capable of forming a tumor at one point in time might change during the progression of the disease. Thus, a tumor may be initiated by a set of mutations leading to transformation of one cell type, but progressive mutations occurring during the evolution of the tumor may result in the acquisition of stem cell properties by a second cell type at a later time. The stem cells within an individual tumor may constitute a moving target, that is, the cells that drive growth at one point in time may not be identical to those doing so at another stage in tumor evolution or during metastasis. Furthermore, the genetic and epigenetic instability that are fundamental properties of tumor biology can induce cellular heterogeneity within the stem and non stem cell populations of the tumor. Evidence was given that specific oncogenes or mutations could play a significant role in determining the target cell that eventually becomes malignant. Animal models will be useful for understanding the origins of cells with the properties expected of cancer stem cells and when and where they arise during cancer initiation and progression (5).

## Two models for cancer stem cell origin

The classical model of cancer formation, termed the stochastic model, defines tumor cells as biologically equivalent. Intrinsic factors, such as signaling pathways and levels of transcription factors, and extrinsic factors, such as the microenvironment, host-specific factors, and immune response, result in varied and unpredictable behavior of the tumor cells. Therefore, tumor-initiating activity cannot be attributed to any specific type of cells. Conversely, the hierarchy model proposes that tumors are made up of biologically distinct types of cells with varying functions and behaviors. Tumor growth can only be initiated by a subset of cells known as cancer stem cells (CSCs), which can self-renew and differentiate to nontumorigenic progeny that comprise the tumor mass. According to present research the both models for CSC of cancer formation is correct (6).

## Preliminary Direction of CSC research: It’s Successful Isolation and Identification by surface Markers

Acquired chemo-resistance has curtailed cancer survival since the dawn of the chemotherapy. Accumulating

evidence suggests a major role for cancer stem cells (CSCs) in chemo-resistance, though their involvement in acquired resistance is still unknown. Cancer stem cells are considered to be the source of tumor development and radiation resistance (7, 8, 9, 10). Successful separation and identification of cancer stem cells are of great challenge for long term culture of CSCs and analysis of antiapoptotic proteins or RNAs expressions or epigenetic regulation of small RNAs. Positive selection is one of the best and most direct ways to isolate target cells from cell suspension (11). CSCs have a set of markers for detection and determination. For instance, CD133 known as Prominin 1 or AC133 is an intermembrane protein and a special surface antigen in blood stem cells whose function is yet to be discovered, but known as a marker for cancer tissues and is used individually or combined with other markers to isolate stem cells from many tumors like brain, breast, ovarian, prostate, colorectal, renal, lung carcinoma etc. (12-17). Surface markers such as ESA, CD44+, are characterized in breast, ovarian, colon, prostate, pancreas or in head and neck cancer tissues while low CD24-, CD 45- found in breast or hepatocellular carcinomas (12-17, 18). The only selected marker identified for T ALL (T-acute Lymphoblastic Leukemia) was CD34+ and further studies on T ALL cell lines have led to the detection of other markers like CD110 (C-MP1), CD90 (ty-1), CD44+, CD49+, CD133+ and the ALDH enzyme in colorectal cancer. ALDH1 is introduced as a stem cell marker. Expression of ALDH1 may be associated with clinic pathologic feature in esophageal squamous cell carcinoma patients (19). Studies on different carcinogenic models conducting worldwide; has gone deep into the level of gene regulation in cancer stem cells has shown that cancer stem cells like breast CSCs (ESA+CD44+CD24-/low, BCSCs) possessing the stem cell properties of self-renewal and multi-directional differentiation are the most fundamental contributors to drug resistance, recurrence and metastasis of different cancers (20).

These above mentioned surface markers can be used to isolate and enrich CSCs in Long term cell culture, by FACS (Fluorescence-activated cell sorting), and MACS (magnetic cell sorting) based cell sorting techniques. Fluroscence phenotyping of cells based on the expression of special cell surface such as CD 24, CD133, ALDH1 and CD44 could also be done. Isolation and long term successful culture of CSCs also could be done with determining its stem-ness properties by various methodologies such as immunofluroscence staining of CSC specific markers or by apoptosis assay or cell migration assay. CSC characteristics can be determined through mRNA and Micro RNAs (miRNA) expression analysis by microarrays, copy number variation, etc. Then phenotypic and genotypic characteristics can be associated with in vitro and in vivo clinical data.

## Role of Micro RNAs in progression or prevention of Cancer Stem Cells with Emphasis on its radiotherapy resistance or sensitivity

### MiRNA an epigenetic regulator of CSC

Micro RNAs (miRNAs) are newly discovered, a class of 22 nucleotide endogenous short non-coding single-stranded RNA molecules. They are important regulators of gene expression with implications in the regulation of critical processes that are deregulated in cancer cells, as proliferation (21) differentiation (22) and apoptosis (23) in recent years. Specific miRNAs play a unique and important regulation role in characteristics of cancer stem cells (24, 25, 26, 27, 28, 29) and can be secreted and stably expressed in animal serum/plasma (30). They have emerged as essential players in the regulation of morphogen and growth factor bio-availability, through non-cell-autonomous mechanisms (31) as well as in governing the crosstalk between tumor cells and their microenvironment (31). It is currently the most important class of gene regulatory molecules at the post transcriptional level in known tumor cells including the regulation of genes with biological characteristics such as radiation tolerance gene. Several studies have shown that ionizing radiations induce changes in miR expression profiles in cells and in preclinical models (33). Yet, the immediate effects of radiotherapy on miR expression and their significance in vivo, if any, are unknown (34). It can be inferred that radiation-specific miRNAs play an important role in the regulation of radiation resistance related genes of cancer stem cells (35).

### Differential Expression of mi-RNAs in Different Carcinogenic Models

Micro RNAs (miRNAs) are involved in cancer pathogenesis by posttranscriptional regulation of gene expression. Many studies have examined the use of miRNAs as cancer diagnostic marker and as anticancer therapy. miRNAs involved in carcinogenesis are classified into oncogenic miRNAs (oncomiRs) and tumor suppressor miRNAs (tumor suppressor miRs) (Fig 1) (29, 36). The primary miRNA (pri-miRNA) transcribed by RNA polymerase II are processed

generally from and cleaved into pre-miRNAs by the nuclear RNase III Drosha, and then the pre-miRNA is transformed to a mature miRNA by Dicer, another RNase III. Eukaryotic translation initiation factors, bind to mRNAs by recognition of the 5' tail cap structure and Poly A-binding protein (PABP) binds to the 3' poly A tail to attract eIF4G to mRNAs, and thus initiating translation by synergistic action of mRNA cap structure and poly A tail. miRNAs negatively regulate gene expression by binding to complementary sequences in the 3'untranslated region (UTR) of a target mRNA, repressing its translation and enhances degradation of the target. The RNA-induced silencing complex (RISC) containing a miRNA binds the 3'-UTR in mRNAs and induces formation of the CCR4-CAF1-NOT complex, a poly A tail-truncating enzyme, resulting in truncation of the downstream poly A tail, reduced binding of translation initiation factors, and repression of translation (37) (Fig 2, 38). Little is known about the specific role of miRNAs. The miRNAs in mammalian cells have an average half-life of around 5 days, 10 times more than that of regular mRNAs (39). These small RNAs are resistant to degradation by RNase A (40), high temperature, extreme pH, and freeze-thaw cycles (41). These characteristics of miRNAs make them suitable to serve as prognostic biomarkers of diseases. The miRNA expression profile can discriminate between normal tissue and tumor tissue and this differential expression can also be used as a prognostic marker for clinical aggressiveness of human cancer (42). miRNAs can act as oncogenes or anti-oncogenes and are involved in tumorigenesis, including chronic lymphocytic leukaemia, paediatric Burkitt's lymphoma, gastric cancer, lung cancer and large-cell lymphoma (43, 44, 45). Different carcinogenic models show implication of different miRNAs. Studies have identified chromosomal alterations, gene expression changes, and aberrant promoter methylation associated with cervical cancer (CC) (46).

## miRNA in Breast Cancer Progression or Prevention

Breast cancer is one of the most common cancers in women and poses a threat to women's health. Breast cancer stem cells (ESA+CD44+CD24-/low, BCSCs) possessing the stem cell properties of self-renewal and multi-directional differentiation are the most fundamental contributors to drug resistance, recurrence and metastasis of breast cancer (47). Previous studies in both breast cancer cells and tissues have shown that BCSCs are cells with an ESA+CD44+CD24-/low phenotype. Research focusing on BCSCs is likely to bring revolutionary changes to understanding of breast cancer; however, a multitude of unresolved issues remain with regard to the molecular basis of carcinogenesis. In further to find out full nature of the involvement of BCSCs in the molecular mechanisms of tumorigenesis or involvement of micro-RNAs (miRNAs) in the function of BCSCs microarray profiling of miRNAs of both ESA+CD44+CD24-low breast cancer stem cells and MCF7 cell lines were done (48). As an important class of regulatory noncoding RNAs, miRNAs have been shown to play important roles in the committed differentiation and self-renewal of embryonic stem cells and adult stem cells (47). The current release (10.0) of miRBase contains 5071 miRNA loci from 58 species (49). miRNA expression profiles of BCSCs and MCF-7 cells using a normalisation factor and clustering, identified differentially expressed 19 miRNAs that fell into two groups (fold change $\geq 4$) (50). Among these 19 miRNAs over-expression of miR-122a plays a role in the genesis of hepatocellular carcinoma by blocking cyclin G1 expression (51). Another study found that G3BP2, one of the potential targets of miR-122a, was more highly expressed in breast cancer tissue than in para-neoplastic tissue.

These studies indicate that miR-122a is likely to be an important gene regulatory factor in cancer cells, even cancer stem cells. On contrary down regulated expression of miR-21in BCSCs, has been reported to have extensive roles and is expressed in embryonic stem cells (52), neuronal cells (53) and several tumor tissues (54, 55) and as an oncogene, targets the tumor suppressor gene. Furthermore, the prediction of potential targets for other BCSC-related miRNAs indicated overlap between the targets of different miRNAs. For example, PLAG1 was a potential target for both miR-224 and miR-200a, and the expression of miR-200a was lower in BCSCs than in MCF-7 cells. In contrast, the expression of miR-224 was higher in BCSCs than in MCF-7 cells.

It is likely that the miRNAs that are over-expressed or under-expressed in BCSCs may regulate common target genes and form a miRNA gene network by cooperating or competing with each other to regulate the development of BCSCs. Moreover, miR-301, miR-296, miR-21 and miR-373* have been reported to be expressed in human embryonic stem cells and other stem cells, indicating that these miRNAs may play a constitutive role in maintaining the biological characteristics of stem cells (56, 57). Future work should include verification of the potential targets of all of the BCSC-related miRNAs identified so far.

## Microarray identify several oncomiRs and tumor suppressor miRs in Cervical Cancer

Cervical cancer is a primary cancer of the uterine cervix in females and has a high incidence and mortality.

By comparing miRNA expression in normal and cancer tissues, many miRNAs with cancer-specific upregulation (oncomiRs) or downregulation (tumor suppressor miRs) have been found in cervical cancer. Among some typical oncomiRs, miR-21 is over expressed in many kinds of cancer and is a negative regulator of expression of the tumor suppressor gene programmed cell death 4 (PDCD4). Expression of *PDCD4* is implicated in apoptosis and also blocks translation and inhibits tumor growth, and thus miR-21 binding to the *PDCD4* 3' UTR enhances cell growth (58). miR-19a and miR-19b are overexpressed in cervical cancer cells and implicated in cytopoiesis of malignant-type HeLa and C33A cells. (59). miR-20 enhances expression of the oncogene tyrosine kinase, non receptor 2 (*TNKS2*). Once *TNKS2* is suppressed, metastasis and invasion of cervical cancer cells are suppressed. However, miR-20 positively regulates *TNKS2*, resulting in enhanced metastasis and invasion (60). miR-133b regulates several signaling pathways facilitating malignant transformation. The latency period of cervical neoplasm is shortened as miR-133b expression is increased, which makes miR-133b a marker for early cervical cancer.

miR-138 is involved in regulation of telomerase, an enzyme that is strongly associated with cell immortalization and carcinogenesis through extension of telomeres in chromosomal ends. Telomerase activity depends on expression of *human telomerase reverse transcriptase (hTERT)*, and miR-138 suppresses the *hTERT* mRNA level and reduces telomerase activity. miR-138 expression in cervical cancer cells is significantly lower than that in normal tissues, which causes telomerase activation and carcinogenesis (61). In HeLa and C33-A cervical cancer cells, overexpression of tumor suppressor miRNA, miR-7 inhibits cell growth and enhances apoptosis, whereas its suppressed expression has opposite effects. miR-7 targets and regulates *X*-linked inhibitor of apoptosis protein (XIAP) (62). miR-17-5p also a tumor suppressor miRNA found in cervical cancer tissues, targets tumor protein p53-induced nuclear protein1 (TP53INP1) and inhibits cell growth, leading to apoptosis. *TP53INP1* plays an important role in stress reactions in cells and miR-17-5p-induced cell growth inhibition is interfered if *TP53INP1* is ectopically expressed (63). Overexpression of miR-125b inhibited cell growth, induced apoptosis, and decreased tumorigenicity by suppression through phosphoinositide 3- kinase mediated antiapoptotic K/Akt/mTOR signaling pathway (64).

Extra cellularly secreted miRNAs in serum can be used as diagnostic markers for cervical cancer diagnosis and treatment because secreted miRNA profiles of cancer patients differ significantly from those of normal volunteers. Reagents for extraction of miRNAs from plasma and serum are available and miRNA profile can be examined by microarray and quantitative RT-PCR revealed specific expression changes in cancer (65). miR-126 and miR-21 are found in serum and are associated with cervical cancer (66). Overexpression of other new candidate miRNA markers such as miR-21, miR-27a, miR-34, miR-34a, and miR-196a were found in squamous cell carcinoma of the cervix (67).

## Differential expression of miRNAs in lung Carcinoma

Larynx Cancer (LCa) is an aggressive neoplasm constituting approximately 1 to 2.5 % of all human cancer cases worldwide (68). Despite notable enhancements in the therapeutic options; treatment outcome, prognosis, and 5-year survival rates for LCa remained almost unchanged in nearly past two decades. Kharas *et al.,* reported microarray profiling of LCa CD133+ enriched CSCs exploring eight differentially expressed miRNA in cancer tisues (69). Among those significantly differentially expressed miRNAs, five were downregulated (miR-26b-5p, miR-200c-3p, miR-203a, miR-223-3p, miR-363-3p) and three were upregulated (miR-328, miR-574-3p, miR-1825). miR-26b, miR-200c, miR-203, and miR- 363-3p were found to have significantly reduced expression in CD133+ larynx CSLCs, whereas miR-1825 were validated to have increased expression in these CD133 enriched LCa cells (70). miR-1825 resides within 20q11.21 chromosomal region, whose amplification displayed increased colony forming potential and decreased apoptosis in human embryonic stem cells and induced pluripotent stem cells (71). Interestingly, 20q11.21 amplification in human embryonic stem cells resulted in acquisition of a gene-expression signature enriched for cancer-associated genes (72). Overexpression of miR-1825 in CD133+ larynx CSLCs and suggest miR-1825 as an important contributor of carcinogenesis.

**Fig.1** Role of miRNA-Regulated Cancer Stem Cells in the Pathogenesis of Human Malignancies

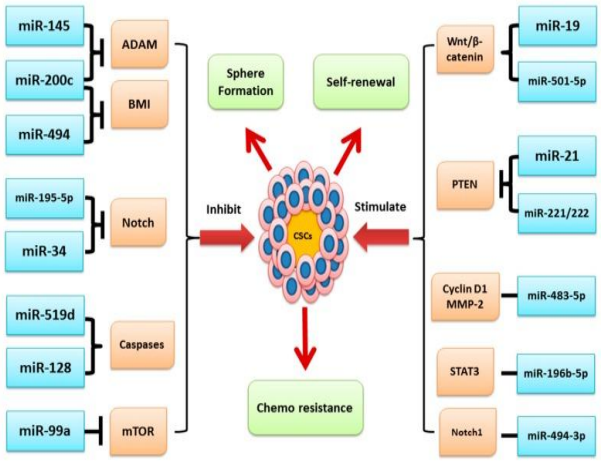
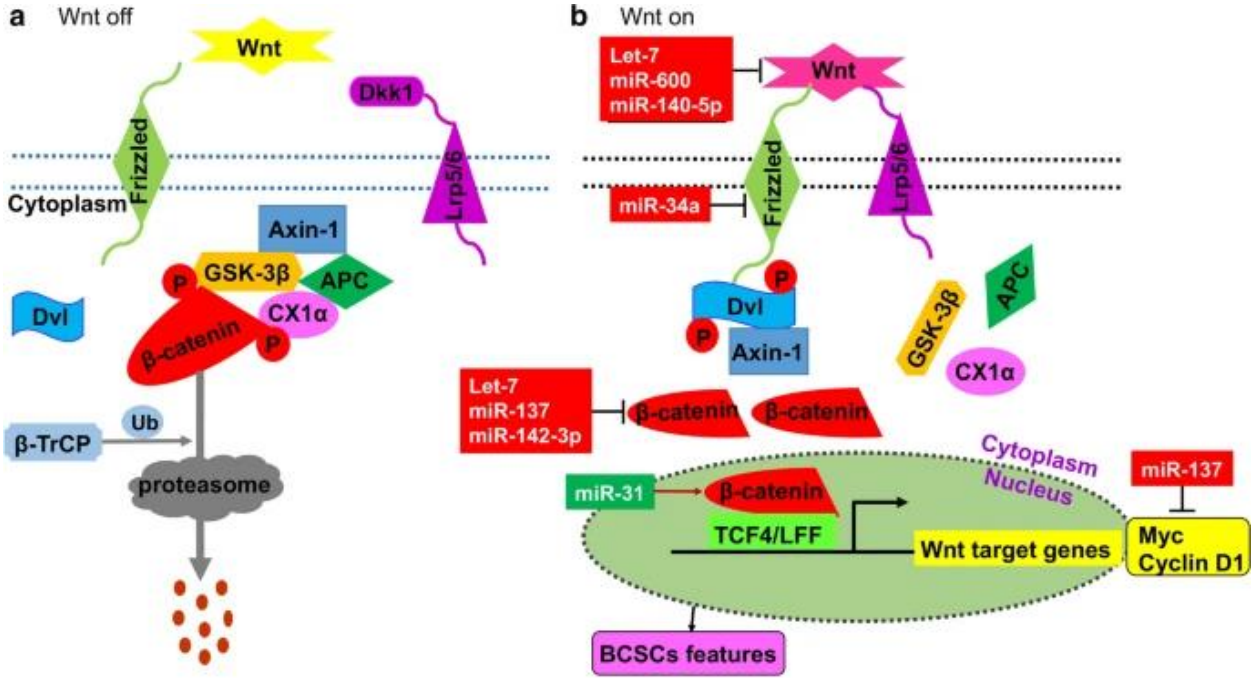



**Fig.2** miRNA-mediated regulation of BCSCs via targeting the Wnt/β-catenin signaling pathway. a "Wnt off". In the absence of Wnt ligands, the destruction complex (Axin-1, GSK-3β, APC, CX1α) is formed. β-catenin is phosphorylated by the destruction complex, thereby targeting it to be degraded by the β-TrCP-mediated ubiquitin proteasome system. b "Wnt on". Wnt ligands bind to the Frizzled/Lrp 5/6 receptors, thus leading to Dvl phosphorylation. Phosphorylated Dvl recruits Axin to the membrane, which destroys the destruction complex and prevents the phosphorylation of β-catenin. Thus, β-catenin accumulates in the cytoplasm and finally moves into the nucleus, where it interacts with TCF4/LEF and/or co-activators and promotes the transcription of Wnt target genes. The immediate targets of several miRNAs are marked.




## MicroRNA in Cell Death

Deficiency in apoptosis is considered to be a major cause of the therapeutic resistance of non small cell lung carcinoma (NSCLC). Apoptosis is activated and inactivated by a variety of genes. It is well accepted that the response to cellular stress factors like DNA damage involves activation of tumor suppressor p53, a sequence-specific transcription factor. Few convincing evidences suggest reactive oxygen species (ROS) generation

triggers activation of p53 (73). The primary function of p53 is to activate transcription of genes that contain p53-binding sites in their promoters. Transcriptional targets of p53 include the proapoptotic B cell lymphoma-2 (Bcl-2) family member Bcl-2 associated X protein (Bax), which migrates to mitochondria from cytosol in response to apoptotic signals, permeabilizes the outer membrane, resulting in release of mitochondrial proteins such as cytochrome c, AIF etc. into the cytosol or nucleus where they are actively involved in the process of caspase activation and protein/DNA degradation (74, 75). Since miRNAs are classified into oncogenic and tumor suppressor miRNAs and the miRNA expression level frequently decrease in human cancer tissues, many miRNAs may have the potential for tumor suppression activity associated with the *p53* gene (76). For example miR- 192, miR-194, and miR-215 are induced by DNA damage in a *p53*-dependent manner, while miR-17-92 cluster are repressed by *p53* under hypoxic conditions (77-78). Screening for miRNAs regulating the *p53* pathway showed that the miR-29 family (miR-29a, miR-29b, and miR-29c) activates the *p53* pathway (79). In addition, miR-122 positively regulates the *p53* pathway via cyclinG1 (80), miR-125b directly inhibits *p53* (81), and miR-21 negatively regulates the *p53* pathway by targeting heterogeneous nuclear ribonucleoprotein K (HNPRK), a positive regulator of the *p53* pathway, and the *p53* homolog, *p63* (82). miRNA can also affect the downstream *p53* pathway, based on the negative regulation of *p53*-induced CDK inhibition (83). More recent investigations identified another tumor suppressor miRNAs of miR 34 families, miR- 34a, miR-34b and miR-34c (83). The epigenetic inactivation of miR-34a has been identified in many common tumor types (lung, breast, colon, kidney, bladder, pancreatic cancer and melanoma) and also in cell lines derived from those tumors. Besides p53 mutation or functional inhibition of the expression of miR-34a, there is evidence that aberrant CpG methylation of the miR-34a promoter can result in concomitant loss of miR-34a expression (84). The importance of miR-34a in cancer is now firmly established and restoration of functional miR-34a can inhibit various cancer cell growths and induce apoptosis. For example, chemically synthesized miR-34a was shown to block tumor growth in NSCLC in vivo (85) and over-expression of miR-34a in bulk or purified CD44 (+ve) prostate cancer cells inhibited clonogenic expansion, tumor regeneration and metastasis (86).

Recently it has been shown that MET, the tyrosine kinase receptor for hepatocyte growth factor (HGF), has a central role in lung cancer development and in acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors; it has been predicted and shown to be the target gene of multiple miRNAs, which play a crucial role in controlling its activity in a stimulatory or inhibitory sense. All members of miR-34 family, targeting more than 77 target mRNAs, were shown to suppress tumor growth and metastasis by inhibiting the processes that stimulate the cancer development, including cell cycle, EMT, metastasis, stemness and by promoting the processes that inhibit carcinogenesis, such as apoptosis (87, 88).

## Micro RNA Mediated Increased or Decreased Sensitivity to Radiation or Chemotherapy of Cancer Stem Cells

Micro RNA (miRNA) is the most important class of gene regulatory molecules currently known in tumor cells. The discovery of miRNA has become another significant progress and research focus of oncology research in recent years including studies on the relationship between miRNAs and radiosensitivity.

Radiotherapy is one of clinically important treatments of cancer. However, the radiation resistance of cancer stem cells is still a difficult problem which seriously affects radiotherapy. Different cancer cells show expression of different up- or down regulated miRNAs which are crucial for playing key role in resistance or sensitivity to chemotherapy and radiotherapy. There are several no of tumor suppressor miRs such as miR-155, miR-214, miR-218, which either increases sensitivity to cisplatin (chemotherapeutic drug), or negatively regulates the EGF-induced epithelial-mesenchymal transition (EMT), inhibits proliferation, metastasis, invasion and finally promots cell death (89-90).

There are reports of many miRNAs being implicated in resistance of cancer stem cells to chemotherapy and radiotherapy. miR-375, miR-181a contributes to acquisition of resistance to chemotherapeutic drug paclitaxel in cervical cancer cells, or increases cellular resistance to radiotherapy through negative regulation of apoptosis (91-92). Not only in cervical cancer, Wang, *et al.,* (2011) reported 12 differently expressed miRNAs in the radiotherapy sensitive and resistant non-small cell lung cancer samples also (93). Comparing with radiotherapy resistant patients, five miRNAs (miRNA-126, miRNA-let-7a, miRNA-495, miRNA-451 and miRNA-128b) were significantly upregulated and seven miRNAs (miRNA-130a, miRNA-106b, miRNA-19b, miRNA-22, miRNA-15b, miRNA-17-5p and miRNA-

21) were greatly down regulated in radiotherapy sensitive group. Further analysis, found that miRNA-126 promoted cancer cells apoptosis induced by irradiation through the PI3K-Akt pathway (94).

A detailed understanding of miRNA mechanisms may also permit targeted therapeutic strategies based on miRNA inhibition or supplementation, as described above. If overexpression of a specific miRNA causes resistance to chemotherapy or radiotherapy, this resistance may be reduced by inhibiting the miRNA function.

Similarly, if down regulation of a miRNA causes resistance; this may be improved by supplementation of this miRNA. Therefore, new combination therapy of miRNA inhibitors or supplementation with chemotherapy or radiotherapy may be developed. Such treatment approaches using miRNAs with distinct expression patterns may be particularly useful in personalized treatment and molecular targeted therapy for several cancers.

## The Future Perspective of Review

The underlying mechanisms beneath the prevention or propagation of cancer stem cell, are not yet completely understood. Therefore, elucidation of genetic and epigenetic circuits regulating the stem cell characteristics of CSCs might help understanding the molecular basis of carcinogenesis.

Therefore, more studies exploring the underlying mechanisms of CSC pathogenesis are urgently needed for better understanding of carcinogenesis development and providing more effective treatment strategies. Currently, studies of miRNA regulation on the radiotherapy resistance level of different types CSCs have not been reported both home and abroad.

Because of the fast, parallel, high-throughput detection characteristics, selection of oligonucleotide microarrays for comparative analysis of miRNA expression profiles in cancer stem cells before and after radiation, with combination of miRNA screening and clustering analysis have gained long term focus in oncology research.

This may lay the foundation for further study of the relationship of miRNA with cancer radiation related biological characteristics and could provide the basic information on the development of cancer stem cell radio sensitizer based on miRNA regulation and targeting.

## Acknowledgement

We are thankful to Dr. Tania das and Dr. Gourishankar Shaw of Dept of Molecular Medicine, Bose Institute, for their valuable concept.

## References

1. Liu Y, Yang R, He Z, Gao W-Q. Generation of functional organs from stem cells. Cell Regen (Lond) 2013; 2:1.
2. Clarke M F, Dick J E, Dirks P B, *et al.*,: Cancer stem cells—perspectives on current status and future directions: AACR Workshop on cancer stem cells. Cancer Res. 2006; 66: 9339-9344.
3. Wicha M S, Liu S, Dontu G. Cancer stem cells: an old idea—a paradigm shift. Cancer Res. 2006; 66:1883-1890.
4. Jordan C T, Guzman M L, Noble M. Cancer stem cells. N Engl J Med. 2006; 355: 1253-1261.
5. Repeat ref 2.5. Michael F. Clarke M F, John E. Dick, Peter B. Dirks, Connie J. Eaves, Catriona H. M. Jamieson, D. Leanne Jones, Jane Visvader, Irving L. Weissman, and Geoffrey M. Wahl. Cancer Stem Cells—Perspectives on Current Status and Future Directions: AACR Workshop on Cancer Stem Cells. Cancer Res 2006; 66: (19).
6. Wicha M S. Cancer Stem Cells: *Current Perspectives, Future Directions.* Oncology Times • 10, 2015
7. Hambardzumyan D, Squatrito M, Holland E C (2006). Radiation resistance and stem-like cells in brain tumors. *Cancer Cell*, 10, 454-6.
8. Blazek E R, Foutch J L, Maki G (2007). Daoy medulloblastoma cells that express CD133 are radioresistant relative to CD133- cells, and the CD133+ sector is enlarged by hypoxia, Int J Radiat. *Oncol Biol Phys*, 67, l-5.
9. Kang M K, Har B I, Ko M H, *et al.*, (2008). Potential identity of multi-potential cancer stem-1ike subpopulation after radiation of cultured brain glioma. *BMC Neurosci*, 9, 15.
10. Ghotra V P, Puigvert J C, Danen E H (2009). The cancer stem cell microenvironment and anti-cancer therapy. *Int J Radiat Biol*, 85, 955-62.
11. O'Brien, C. A., Pollett, A., Gallinger, S. and Dick, J. E. (2007) A Human Colon Cancer Cell Capable of Initiating Tumour Growth in Immunodeficient Mice. *Nature*, 445, 106-110.
12. Patrawala, L., Calhoun, T., Schneider-Broussard, R., Li, H., Bhatia, B., Tang, S., Reilly, J.G., Chandra, D., Zhou, J., Claypool, K., Coghlan, L.

and Tang, D.G. (2006) Highly Purified CD44+ Prostate Cancer Cells from Xenograft Human Tumors Are Enriched in Tumorigenic and Metastatic Progenitor Cells. *Oncogene*, 25, 1696-1708.

13. Al-Hajj, M., Wicha, M. S., Benito-Hernandez, A., Morrison, S. J. and Clarke, M. F. (2003) Prospective Identification of Tumorigenic Breast Cancer Cells. *Proceedings of the National Academy of Sciences of the United States of America*, 100, 3983-3988.
14. Klonisch, T., Wiechec, E., Hombach-Klonisch, S., Ande, S. R., Wesselborg, S., Schulze-Osthoff, K. and Los, M. 2008. Cancer Stem Cell Markers in Common Cancers-Therapeutic Implications. *Trends in Molecular Medicine*, 14, 450-460.
15. Singh, S. K., Hawkins, C., Clarke, I. D., Squire, J. A., Bayani, J., Hide, T., Henkelman, R. M., Cusimano, M. D. and Dirks, P. B. (2004) Identification of Human Brain Tumour Initiating Cells. *Nature*, 432, 396-401.
16 Annabi, B., Rojas-Sutterlin, S., Laflamme, C., Lachambre, M. P., Rolland, Y., Sartelet, H. and Beliveau, R. (2008) Tumor Environment Dictates Medulloblastoma Cancer Stem Cell Expression and Invasive Phenotype. *Molecular Cancer Research*, 6, 907-916.
17. Shien, K., Toyooka, S., Ichimura, K., Soh, J., Furukawa, M., Maki, Y., Muraoka, T., Tanaka, N., Ueno, T., Asano, H., Tsukuda, K., Yamane, M., Oto, T., Kiura, K. and Miyoshi, S. (2012) Prognostic Impact of Cancer Stem Cell-Related Markers in Non-Small Cell Lung Cancer Patients Treated with Induction Chemoradiotherapy. *Lung Cancer*, 77, 162- 167.
18. Boman, B. M. and Wicha, M. S. (2008) Cancer Stem Cells: A Step toward the Cure. *Journal of Clinical Oncology*, 26, 2795-2799.
19. Ouhtit, A., Abd Elmageed, Z. Y., Abdraboh, M. E., Lioe, T. F. and Raj, M. H. G. (2007) *In Vivo* Evidence for the Role of CD44s in Promoting Breast Cancer Metastasis to the Liver. *The American Journal of Pathology*, 171, 2033-2039.
20. Zheng Q, Zhang M, Zhou F, Zhang L and Meng X (2021) The Breast Cancer Stem Cells Traits and Drug Resistance. REVIEW article Front. Pharmacol., https://doi.org/10.3389/fphar.2020.599965
21. Wu, N., Liu, X., Xu, X., Fan, X., Liu, M., Li, X., Zhong, Q. and Tang, H. (2011) MiR- 373, a novel regulator of PPP6C, functions as an oncogene in hepatocellular carcinoma. FEBS J. 278, 2044–2054.
22. Annibali, D., Gioia, U., Savino, M., Laneve, P., Caffarelli, E. and Nasi, S. (2012) A new module in neural differentiation control: two microRNAs upregulated by retinoic acid, miR-9 and -103, target the differentiation inhibitor ID2. PLoS ONE 7, e40269.
23. Chan, J. A., Krichevsky, A. M. and Kosik, K. S. (2005) MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. Cancer Res. 65, 6029–6033.
24. Schetter A J, Leung S Y, Sohn J J (2008). MicroRNA expression profiles associated with prognosis and therapeutic outcome in colon adenocarcinoma. *JAMA*, 299, 425-36.
25. Avissar M, McClean M D, Kelsey K T, Marsit C J (2009). MicroRNA expression in head and neck cancer associates with alcohol consumption and survival. *Carcinogenesis*, 30, 2059-63.
26. Hime G R, Somers W G (2009). Micro-RNA mediated regulation of proliferation, self-renewal and differentiation of mammalian stem cells. *Cell Adh Migr*, 3, 425-32.
27. Mueller D W, Bosserhoff A K (2009). Role of miRNAs in the progression of malignant melanoma. *Br J Cancer*, 101, 551-6.
28. Valeri N, Croce C M, Fabbri M (2009). Pathogenetic and clinical relevance of microRNAs in colorectal cancer. *Cancer Genomics Proteomics*, 6, 195-204.
29. Khan A Q, Ahmed E I, Elareer N R, Junejo K, Steinhoff M, Uddin S (2019). Role of miRNA-Regulated Cancer Stem Cells in the Pathogenesis of Human Malignancies. Review Cells 8(8): 840.
30. Wang S H, Lu L, Fan Y, Wicha M S, Cao Z, Chang A E *et al.*, Characterization of a novel transgenic mouse tumor model for targeting HER2+ cancer stem cells. Int J Biol Sci 2013; 10: 25–32.
31. Inui M, Montagner M, Piccolo S. miRNAs and morphogen gradients. Curr Opin Cell Biol 2012; 24: 194–201.
32. Redis R S, Calin S, Yang Y, You M J, Calin G A. Cell-to-cell miRNA transfer: from body homeostasis to therapy. Pharmacol Ther 2012; 136: 169–174.
33. Metheetrairut C, Slack F J. MicroRNAs in the ionizing radiation response and in radiotherapy. Curr Opin Genet Dev 2013; 23: 12–19.
34. Fabris L, Berton S, Citron F, D'Andrea S, Segatto I, Nicoloso M S, Massarut S, Armenia J, Zafarana G, Rossi S, Ivan C, Perin T, Vaidya J S, Avanzo

M, Roncadin M, Schiappacassi M, Bristow R G, Calin G, Baldassarre G and Belletti B. Radiotherapy-induced miR-223 prevents relapse of breast cancer by targeting the EGF pathway. Oncogene (2016) 35, 4914–4926

35. Huang C X, Zhu Y, Duan G L, Yao J F, Li ZY, Li D, Wang Q Q. Screening for MiRNAs Related to Laryngeal Squamous Carcinoma Stem Cell Radiation. *Asian Pac J Cancer Prev*, 2013 14 (8), 4533-4537.
36. Banno K, Yanokura M, Kisu I, Yamagami W, Susumu N, and Aoki D, "MicroRNAs in endometrial cancer," *International Journal of Clinical Oncology*, 2013 18, 186–192,.
37. Gantier M P, McCoy C E, Rusinova I *et al.*, Analysis of microRNA turnover in mammalian cells following Dicer1 Ablation. Nucleic Acids Research 2011, 39: 5692–5703.
38. Niu T, Zhang W and Xiao W. MicroRNA regulation of cancer stem cells in the pathogenesis of breast cancer. Cancer Cell Int. 2021; 21: 31.
39. Li J, Smyth P, Flavin R *et al.*, Comparison of miRNA expression patterns using total RNA extracted from matched samples of formalin-fixed paraffin-embedded (FFPE) cells and snap frozen cells. BMC Biotechnology 2007, 7: 36.
40. Lee J W, Choi C H, Choi J J *et al.*, Altered microRNA expression in cervical carcinomas. Clinical Cancer Research 2008, 14: 2535–2542.
41. He L, Thomson J M, Hemann M T, Hernando-Monge E, Mu D, Goodson S, Powers S, Cordon-Cardo C, Lowe SW, Hannon GJ, Hammond SMA: MicroRNA polycistron as a potential human oncogene. Nature 2005, 435(7043): 828-833.
42. Iorio M V, Ferracin M, Liu C G, Veronese A, Spizzo R, Sabbioni S, Magri E, Pedriali M, Fabbri M, Campiglio M, Ménard S, Palazzo J P, Rosenberg A, Musiani P, Volinia S, Nenci I, Calin G A, Querzoli P, Negrini M, Croce C M. MicroRNA gene expression deregulation in human breast cancer. Cancer Res 2005, 65(16):7065-7070.
43. Gregory R I, Shiekhattar R: MicroRNA biogenesis and cancer. Cancer Res 2005, 65(9): 3509-3512.
44. Wilting S M, Snijders P J F, Verlaat W *et al.*, Altered microRNA expression associated with chromosomal changes contributes to cervical carcinogenesis. Oncogene 2012.
45. Ref 13 repeat 45. Al-Hajj M, Wicha M S, Benito-Hernandez A, Morrison S J, Clarke M F: Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci USA 2003, 100(7):3983-3988.
46. Shcherbata H R, Hatfield S, Ward E J, Reynolds S, Fischer K A, Ruohola-Baker H. The MicroRNA pathway plays a regulatory role in stem cell division. Cell Cycle 2006, 5(2):172-175.
47. Griffiths-Jones S, Saini H K, van Dongen S, Enright A J: Tools for microRNA genomics. Nucleic Acids Res 2008, 36:D154-D158.
48. Sun J G, Liao R X, Qiu J, Jin J, Wang X X, Duan Y Z, Chen F L, Hao P, Xie Q C, Wang Z X, Li D Z, Chen Z T, Zhang S X. Microarray-based analysis of micro RNA expression in breast cancer stem cells. Journal of Experimental & Clinical Cancer Research 2010, 29:174.
49. Gramantieri L, Ferracin M, Fornari F, Veronese A, Sabbioni S, Liu C G, Calin G A, Giovannini C, Ferrazzi E, Grazi G L, Croce C M, Bolondi L, Negrini M: Cyclin G1 is a target of miR-122a, a microRNA frequently downregulated in human hepatocellular carcinoma. Cancer Res 2007, 67(13):6092-6099.
50. Suh M R, Lee Y, Kim J Y, Kim S K, Moon S H, Lee J Y, Cha K Y, Chung H M, Yoon H S, Moon S Y, Kim V N, Kim K S: Human embryonic stem cells express a unique set of microRNAs. Dev Biol 2004, 270(2):488-498.
51. Dostie J, Mourelatos Z, Yang M, Sharma A, Dreyfuss G: Numerous microRNPs in neuronal cells containing novel microRNAs. RNA 2003, 9(2):180-186.
52. Kasashima K, Nakamura Y, Kozu T: Altered expression profiles of microRNAs during TPA-induced differentiation of HL-60 cells. Biochem Biophys Res Commun 2004, 322(2):403-410.
53. Michael M Z, O'Connor S M, van Holst Pellekaan N G, Young G P, James R J: Reduced accumulation of specific microRNAs in colorectal neoplasia. Mol Cancer Res 2003, 1(12):882-891.
54. Houbaviy H B, Murray M F, Sharp P A: Embryonic stem cell-specific MicroRNAs. Dev Cell 2003, 5(2):351-358.
55. Greco S J, Rameshwar P: MicroRNAs regulate synthesis of the neurotransmitter substance P in human mesenchymal stem cell-derived neuronal cells. Proc Natl Acad Sci USA 2007, 104(39):15484-15489.
56. Yao Q, Xu H, Zhang Q Q, Zhou H, and Qu L H. MicroRNA-21 promotes cell proliferation and down-regulates the expression of programmed cell death 4 (PDCD4) in HeLa cervical

carcinoma cells. Biochemical and Biophysical Research Communications 2009, 388: 539–542,.

57. Xu X M, Wang X B, Chen M M *et al.,* MicroRNA-19a and -19b regulate cervical carcinoma cell proliferation and invasion by targeting CUL5. Cancer Letters 2012, 322: 148–158,.
58. Kang H W, Wang F, Wei Q *et al.,* miR-20a promotes migration and invasion by regulating TNKS2 in human cervical cancer cells. FEBS Letters 2012, 586: 897–904.
59. Chakrabarti M, Banik N L, Ray SK. miR-138 overexpression is more than hTERT knockdown to potentiate apigenin for apoptosis in neuroblastoma in vitro and in vivo. Experimental Cell Research 2013, 319: 1575–1585.
60. Liu S, Zhang P, Chen Z, Liu M, Li X, and Tang H. Micro-RNA-7 downregulates XIAP expression to suppress cell growth and promote apoptosis in cervical cancer cells. FEBS Letters 2013, 587: 2247–2253,.
61. Wei Q, Li YX, Liu M, Li X, and Tang H. MiR-17-5p targets TP53INP1 and regulates cell proliferation and apoptosis of cervical cancer cells. IUBMB Life 2012, 64: 697–704.
62. Cui F, li X, Zhu X. *et al.,* MiR-125b inhibits tumor growth and promotes apoptosis of cervix cancer cells by targeting phosphoinositide 3-kinase catalytic subunit delta. Cellular Physiology and Biochemistry 2012, 30: 1310–1318.
63. Kosaka N., Iguchi H., and Ochiya T. Circulating microRNA in body fluid: a new potential biomarker for cancer diagnosis and prognosis. Cancer Science 2010, 101: 2087–2092.
64. Gilad S, Meiri E, Yogev Y. *et al.,* Serum microRNAs are promising novel biomarkers. PLoS One 2008, 3: e3148.
65. Mitchell P S, Parkin R K, Kroh E M *et al.,* Circulating micro RNAs as stable blood-based markers for cancer detection. Proceedings of the National Academy of Sciences of the United States of America vol. 105, no. 30, pp. 10513–10518, 2008.
66. Lawrie C H, Gal S, Dunlop H M *et al.,* Detection of elevated levels of tumour-associated microRNAs in serum of patients with diffuse large B-cell lymphoma. British Journal of Haematology 2008, 141: 672–675.
67. Gocze K, Gombos K, Juhasz K *et al.,* Unique micro RNA expression profiles in cervical cancer. Anticancer Research 2013, 33: 2561–2567.
68. Rudolph E, Dyckhoff G, Becher H, Dietz A, Ramroth H. Effects of tumour stage, comorbidity and therapy on survival of laryngeal cancer patients: a systematic review and a meta-analysis. Eur Arch Otorhinolaryngol. 2011; 268: 165–79.
69. Farhadieh R D, Rees C G, Yang J L, Salardini A, Russell P, Smee R. Radiotherapy in larynx squamous cell carcinoma is not associated with an increased diagnosis of second primary tumours. Clin Oncol (R Coll Radiol). 2009;21:315–9.
70. Karatas O F, Suer I, Yuceturk B, Yilmaz M, Oz B, Guven G, Cansiz H, Creighton C J, Ittmann M, and Ozen M. Identification of microRNA profile specific to cancer stem-like cells directly isolated from human larynx cancer specimens. BMC Cancer (2016) 16:853
71. Nguyen H T, Geens M, Mertzanidou A, Jacobs K, Heirman C, Breckpot K, Spits C. Gain of 20q11.21 in human embryonic stem cells improves cell survival by increased expression of Bcl-xL. Mol Hum Reprod. 2014, 20:168–77.
72. Werbowetski-Ogilvie T E, Bossé M, Stewart M, Schnerch A, Ramos-Mejia V, Rouleau A, Wynder T, Smith M J, Dingwall S, Carter T, *et al.,* Characterization of human embryonic stem cells with features of neoplastic progression. Nat Biotechnol. 2009, 27: 91–7.
73. Liu B, Chen Y and St. Clair, D. K. ROS and p53: a versatile partnership. Free Radical Biol. Med. 2008, 44: 1529–1535.
74. Roos W. P. and Kaina, B. DNA damage-induced cell death by apoptosis. Trends Mol. Med. 2006, 12: 440–450.
75. LeBras M, Rouy I and Brenner C. The modulation of interorganelle cross-talk to control apoptosis. Med. Chem. 2006, 2: 1–12.
76. Georges S A, Biery M C, Kimet S Y *et al.,* Coordinated regulation of cell cycle transcripts by p53-inducible microRNAs, miR- 192 and miR-215. Cancer Research 2008, 68: 10105–10112.
77. Braun C J, Zhang X, Savelyeva I *et al.,* p53-responsive microRNAs 192 and 215 are capable of inducing cell cycle arrest," Cancer Research 2008, 68: 10094–10104.
78. Yan H L, Xue G, Mei Q *et al.,* Repression of the miR-17-92 cluster by p53 has an important function in hypoxia-induced apoptosis. EMBO Journal 2009, 28: 2719–2732.
79. Park S Y, Lee J H, Ha M, Nam J W, and Kim V N. miR- 29 miRNAs activate p53 by targeting p85$\alpha$

and CDC42. Nature Structural and Molecular Biology 2009, 16: 23–29.

80. F. Fornari, L. Gramantieri, C. Giovannini *et al.*, "MiR-122/cyclin G1 interaction modulates p53 activity and affects doxorubicin sensitivity of human hepatocarcinoma cells," *Cancer Research*, vol. 69, no. 14, pp. 5761–5777, 2009.
81. M. T. Le, C. Teh, N. Shyh-Chang *et al.*, "MicroRNA-125b is a novel negative regulator of p53," *Genes and Development*, vol. 23, no. 7, pp. 862–876, 2009.
82. T. Papagiannakopoulos, A. Shapiro, and K. S. Kosik, "Micro-RNA-21 targets a network of key tumor-suppressive pathways in glioblastoma cells," *Cancer Research*, vol. 68, no. 19, pp. 8164–8172, 2008.
83. P. M. Voorhoeve, C. le Sage, M. Schrier *et al.*, "A genetic screen implicates miRNA-372 and miRNA-373 as oncogenes in testicular germ cell tumors," *Cell*, vol. 124, no. 6, pp. 1169–1181, 2006.
84. Samik Chakraborty, Minakshi Mazumdar, Shravanti Mukherjee, Pushpak Bhattacharjee, Arghya Adhikary, Argha Manna, Sreeparna Chakraborty, Poulami Khan, Aparna Sen, Tanya Das. Restoration of p53/miR-34a regulatory axis decreases survival advantage and ensures Bax-dependent apoptosis of non-small cell lung carcinoma cells. FEBS Letters 588 (2014) 549–559
85. Lodygin, D., Tarasov, V., Epanchintsev, A., Berking, C., Knyazeva, T., Körner, H., Knyazev, P., Diebold, J. and Hermeking, H. (2008) Inactivation of miR-34a by aberrant CpG methylation in multiple types of cancer. Cell Cycle 7, 2591– 2600.
86. Wiggins, J. F., Ruffino, L., Kelnar, K., Omotola, M., Patrawala, L., Brown, D. and Bader, A. G. (2010) Development of a lung cancer therapeutic based on the tumor suppressor microRNA-34. Cancer Res. 70, 5923–5930.
87. Liu, C., Kelnar, K., Liu, B., Chen, X., Calhoun-Davis, T., Li, H., Patrawala, L., Yan, H., Jeter, C., Honorio, S., Wiggins, J.F., Bader, A.G., Fagin, R., Brown, D. and Tang, D.G. (2011) The microRNA miR-34a inhibits prostate cancer stem cells and metastasis by directly repressing CD44. Nat. Med. 17, 211–215.
88. Rokavec M, Li H, Jiang L, *et al.*, The p53/miR-34 axis in development and disease. J Mol Cell Biol 2014;6: 214-30.
89. C. Lei, Y. Wang, Y. Huang *et al.*, "Up-regulated miR155 reverses the epithelial-mesenchymal transition induced by EGF and increases chemo-sensitivity to cisplatin in human Caski cervical cancer cells," *PloS One*, vol. 7, no. 12, Article IDe52310, 2012.
90. F. Wang, M. Liu, X. Li, and H. Tang, "MiR-214 reduces cell survival and enhances cisplatin-induced cytotoxicity via downregulation of Bcl2l2 in cervical cancer cells," *FEBS Letters*, vol. 587, no. 5, pp. 488–495, 2013.
91. J. Li, Z. Ping, and H. Ning, "MiR-218 impairs tumor growth and increases chemo-sensitivity to cisplatin in cervical cancer," *International Journal of Molecular Sciences*, vol. 13, no. 12, pp.16053–16064, 2012.
92. Y. Shen, P. Wang, Y. Li *et al.*, "miR-375 is upregulated in acquired paclitaxel resistance in cervical cancer," *British Journal of Cancer*, vol. 109, no. 1, pp. 92–99, 2013.
93. G. Ke, L. Liang, J. M. Yang *et al.*, "MiR-181a confers resistance of cervical cancer to radiation therapy through targeting the proapoptotic PRKCD gene," *Oncogene*, vol. 32, no. 25, pp. 3019–3027, 2013.
94. Wang X C, Du L Q, Tian L L, *et al.*, (201l). Expression and function of miRNA in postoperative radiotherapy sensitive and resistant patients of non-small cell lung cancer. *Lung Cancer*, 72, 92.

**How to cite this article:**

Suranjana Haldar and Atish Haldar. 2021. Cancer Stem Cells: It's Future Perspective by Defining its Radiation Sensitivity and Resistivity through Differentially Regulated Expression of Micro-RNAs. *Int.J.Curr.Res.Aca.Rev.* 9(09), 7-18. doi: https://doi.org/10.20546/ijcrar.2021.909.002