Cancer Stem-Cell Related miRNAs: Novel Potential Targets for Metastatic Prostate Cancer

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Abstract: Globally Prostate Cancer is the second most commonly diagnosed and sixth leading cause of Cancer mortalities in men worldwide but currently there is no cure for metastatic castration-resistant prostate cancer (CRPC). Chemoresistance and metastasis are the main causes of treatment resistance and mortality in Prostate Cancer patients. Although several advances have been made to control yet there is an urgent need to investigate the mechanisms and pathways for chemoresistance and prostate cancer (PCa) metastasis. Cancer stem cells (CSCs), a sub-population of cancer cells characterised by self-renewal and tumor initiation, have gained intense attention as they not only play a crucial role in cancer relapse but also contribute substantially to chemoresistance. Contributing to the role of CSCs are the miRNAs which are known key regulators of the posttranscriptional regulation of genes involved in a wide array of biological processes including tumorigenesis. The altered expressions of miRNAs have been associated with not only with tumor development but also with invasion, angiogenesis, drug resistance, and metastasis. Thus identification of signature miRNA associated with EMT and CSCs would provide a novel therapeutic strategy for the improvement of current treatment thus leading to increase in patient's survival.

Keywords: Cancer stem cells, Epithelial to Mesenchymal Transition, Metastasis, MicroRNA.

INTRODUCTION

Prostate Cancer has become a major health burden in the industrialized world accounting for three fourths of the registered cancer cases during the last decades of the twentieth century [1]. According to the WHO Globocan 2012 report, Prostate Cancer is expected to grow to approximately 2 million new cases and 50000 mortalities by 2030 with a five year prevalence of approximately 25.2% [2]. Disease mortality is primarily due to metastatic spread from the organ confined stage highlighting the urgent need to identify factors involved in this progression. Epithelial to mesenchymal transition (EMT) is an intrinsic event during progression of metastatic cancer. Researchers have showed Wnt, Notch and Hedgehog signaling pathways to be the most common pathways involved in EMT in Cancers by regulating expression of cancer stem cell related miRNAs. MicroRNAs are small non-coding endogenously expressed RNA molecules that are known to regulate of biological processes by altering gene expression at the post transcriptional level. The role of miRNAs in control of tumor growth and progression has been shown by a growing number of evidences. MicroRNAs have also been seen to play crucial roles in maintaining dynamic balance between EMT and MET respectively, collectively termed as "metastamirs" [3]. These pathways are known to be primarily involved in embryonic development, organogenesis, stem cell proliferation and angiogenesis [4-5]. Thus it is imperative to identify regulatory pathways as well as cancer stem cell related miRNAs which would eventually lead to identification of sensitive and specific biomarkers that could facilitate early detection as well as metastatic stages of Prostate Cancer.

EPITHELIAL TO MESENCHYMAL TRANSITION IN CANCER

Epithelial to mesenchymal transition (EMT) is a trans-differentiation process which is crucial during embryogenesis, wound repair, organ remodelling and also tumor progression [6]. EMT is associated with various cellular properties such as altered morphology, migration, invasion and stemness [7]. In cancer, EMT is integral in uncontrolled tissue repair, organ fibrosis, induction of tumor growth, angiogenesis and especially metastasis [8].

Kalluri and Weinberg described EMT as epithelial cells being connected to each other and linked to the extracellular matrix by intracellular junctions (adherens and tight junctions, desmosomes) which eventually acquire mesenchymal characteristics and can invade and metastasize among other biological processes [9]. These circadian phenotype changes should be reversible in nature so that mesenchymal cells can revert back to epithelial phenotype and hence eventually form macroscopic tumors in different areas [10]. EMT is hence marked by downregulation of

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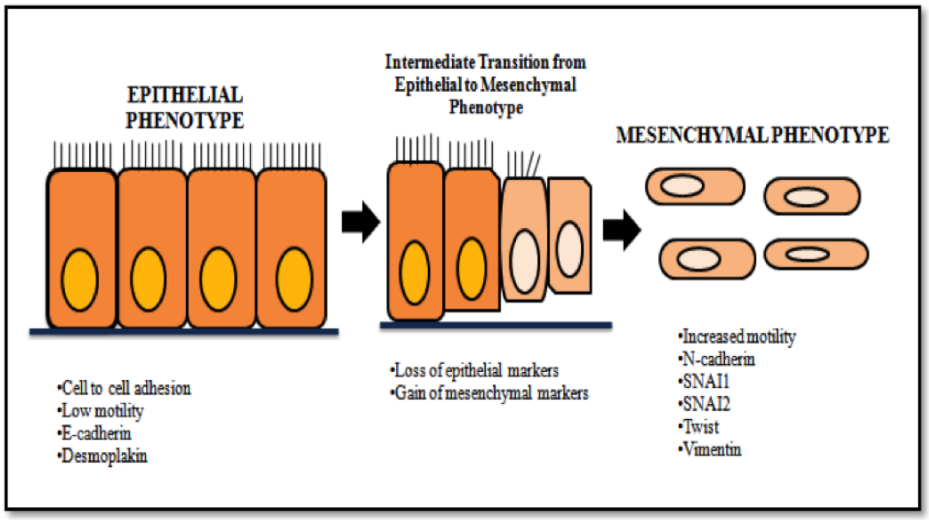

Figure 1: Epithelial to Mesenchymal Transition.

epithelial markers (E-cadherin) and upregulation of mesenchymal markers (N-cadherin and Vimentin) thereby leading to increased migratory capacity and invasiveness. During EMT, E-cadherin gets replaced by N-cadherin in a process known as 'Cadherin switching' [11-12]. Reported markers include extracellular markers (Fibronectin, Vitronectin), cellular localization (Vimentin, E-cadherin), Cellular matrix proteins (E-Cadherin, Claudin, Occludins) and cytoplasmic proteins (Cytokeratins, Vimentins) [13-16].

CANCER STEM CELLS

Majority of cells in solid tumors have limited self-renewal ability and are non-tumorigenic. Only a small subpopulation of cancer cells exhibit ability of extensive self-renewal and tumor formation. This small sub-population is called cancer stem cells (CSCs), or cancer initiating cells (CICs), or tumor stem cells (TSCs) [17-18].

The concept that cancer might evolve from a small sub population of cells with stem cells like properties was proposed about 150 years ago [19-20]. The leukemic stem cells (LSCs) were the first CSCs described as in human Acute Myeloid Leukemia (AML) [21-22]. It was demonstrated by Bonnet and Dick that a subpopulation of CD34+/CD38-AML cells displayed differentiation potential as well as underwent proliferation and self renewal. These LSCs were able to give rise to heterogeneous population in NOD/SCID (non-obese diabetic/severe combined immunodeficiency) mice [23]. Since then various researchers have validated the presence of CSCs which is further strengthened by the recent developments in detecting technologies.

Two models have been proposed to explain tumor heterogeneity: the stochastic and hierarchical models (Figure **2**). The stochastic model proposed that all cells within a tumor are biologically homogenous and exhibit equal capacity to regenerate the tumor however the hierarchical model (also known as the CSC model) suggested that only a small subpopulation of tumor cells possesses the capacity to regenerate the tumor [24-25] and the tumor cells can be separated into tumor initiating and non tumor initiating cells. CSCs (tumor-initiating cells) are defined by their capacity for self-renewal, potential to differentiate into any cells in a tumor, and exhibit proliferative capacity [26].

Thus common characteristics exhibited by Cancer Stem Cells are:

(1) Self-renewal ability (Asymmetric divisions): This leads to generation of quiescent cancer stem cells and committed progenitors [27]. This self renewal ability of CSCs is regulated by signaling pathways such as, Wnt, Sonic Hedgehog, Notch, and Polycomb genes (BMI-1 and EZH2);

(3) Extended telomeres and telomerase activity: CSCs exhibit extended telomeres and telomerase activity due to which they have increased life span;

(4) ATP-binding cassette (ABC) transporters: CSCs express the ABC transporters thus providing cellular resistance against specific growth-inhibitory drugs;

(5) Surface receptor expression: They express surface receptors such as, c-kit, c-met, LIF-R,

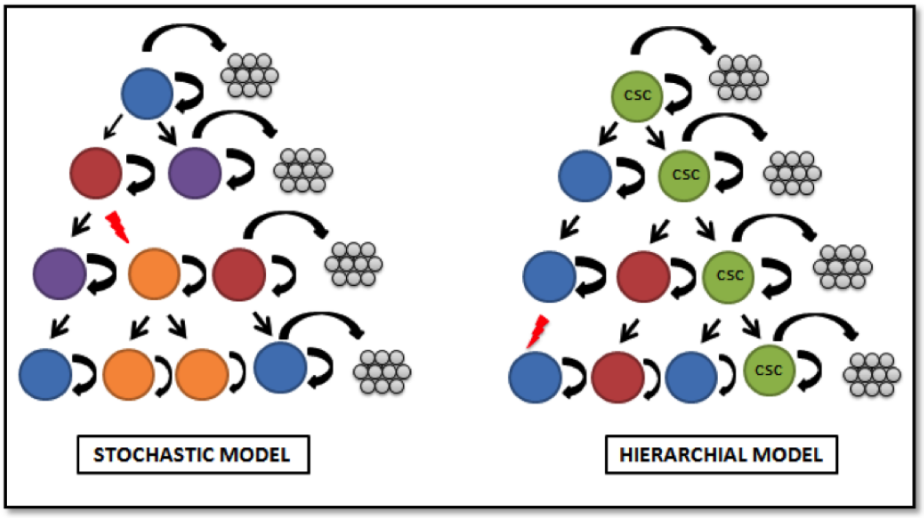

Figure 2: Tumor Heterogeneity Model.

CD133, and CXCR4 which are known stem cell markers and have been associated with metastasis;

(6) Tumor suppressors: Tumor suppressors, such as p53, p16INK4a, and p19ARF inhibit cancer cell proliferation as well as promote their self-renewal [28-29].

All these characteristics are similar to the stem cell characteristics thus indicating common molecular mechanisms for example, molecular pathways, which play a critical role in controlling stem cell self-renewal such as Wnt, Notch and Hedgehog pathways are often dysregulated in a number of tumors [30] and eventually contribute to chemoresistance and radio resistance during tumor therapy [31-33].

CANCER STEM CELLS IN CaP/PCa CHEMORESISTANCE

The cellular origins of CaP have been attributed to terminally differentiated luminal cells by various researchers, [34] however there are increasing evidences which supports the existence of CSCs in CaP [35-39].

During androgen deprivation therapy, the androgen levels are depleted and some epithelial cells die. However, consequently during PCa progression i.e.

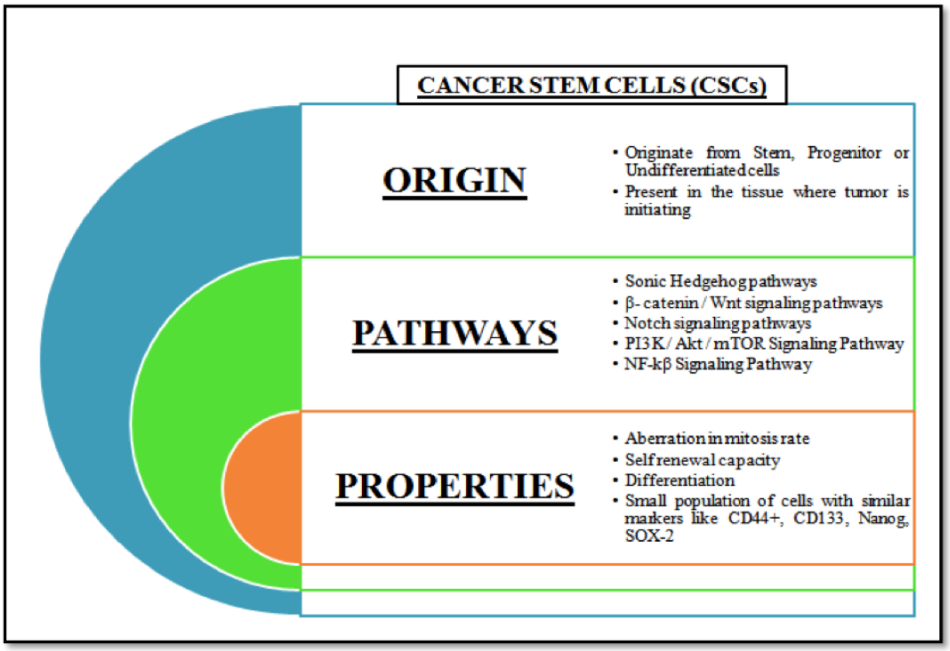

Figure 3: Properties of Cancer Stem Cells.

during metastasis some epithelial cells get renewed which exhibit stem cell like properties in PCa tissue [40]. These CSCs being self renewable potentially lead to tumor development and metastasis of Prostate cancer tissues [41]. These cancer stem cells have been seen to repopulate in tumor cells to distant sites thus further supporting their potential role in metastasis [42].

CSCs and EMT

Various researchers have reported that EMT and CSCs are primary reasons for drug resistance in cancer including Castration Resistant Prostate Cancer (CRPC) which is being supported by studies reporting closely associated signatures of both EMT as well as CSCs

In a research carried out by Mani *et al*., in 2008 it has been shown that Human Mammary Epithelial cells (HMLEs) undergoing EMT had CD44 ^{high} / CD 42 ^{low} phenotype. Also Twist or Snail induced EMT in HMLEs led to a mesenchymal fibroblastic appearance, along with upregulation of mesenchymal markers (N-cadherin, Vimentin and Fibronectin) and downregulation of epithelial markers (E-cadherin etc.) [43].

In another study by Kong *et al.* [44] it was reported that PC3 prostate cancer cells which are forced to express PDGF-D display EMT characteristics. These cells not only showed cancer stem-like cell characteristics after over-expression of pluripotency genes, such as the Nanog, Oct4, Sox2, Lin28 but also showed activation of polycomb repressor complex, which is associated with increased clonogenic and prostasphere forming capacity both *in vitro* and tumorigenicity *in vivo*.

Besides this several researchers have reported that both EMTs and CSCs self renewal potentials are driven by same regulatory pathways such as Wnt, Notch and Hedgehog [45-48].

MicroRNAs, Cancer Stem Cells and Cancer

MicroRNAs (miRNAs) are small non-coding regulatory RNAs of approximately 18-20 nucleotides in length which bind to the 3' untranslated region of their mRNA targets resulting in their degradation or translation repression thus regulate self renewal, differentiation, and differentiation of cells [49].

Recent researches have concluded presence of distinct subpopulation of cancer cells with properties of self renewal and tumor initiation / maintenance thereby acting as Cancer Stem Cells (CSCs). These acquired abnormalities allow them to escape the stem cell niche and reach stage of unlimited self renewal. This may lead to silencing of some crucial regulatory genes. Studies suggest that miRNAs being implicated in RNAi pathway negatively regulate the gene and protein expression level at the post transcriptional level [50]. This certain abnormal miRNA expression level affects cancer stem cells dysregulation, and thus their unlimited self renewal and cancer progression. Therefore, miRNA expression is very vital for cancer stem cell dysregulation [51]. Emerging evidences show miRNAs functioning as oncogenes or tumor suppressors, being involved in cancer proliferation, differentiation, apoptosis and metastasis. Therefore, microRNA-based therapeutics which can rectify the aberrant transcription of genes in cancer and which can especially target CSCs hold a great potential in cancer therapy [52].

Evidences of miRNAs in EMT during Progression of PCa

Current evidences have shown microRNAs to play a crucial role during metastasis in cancer primarily through regulating Epithelial to Mesenchymal Transition in various cancers. As discussed above changes in expressions of Snail, Slug, Twist, Zeb1, Zeb2, E-cadherin and Vimentin are considered as hallmarks of EMT phenotype. More recently, miRNAs have evolved as potential biomarkers for EMT during metastasis in cancer.

miR-200 family (miR-200a, 200b, 200c, 141 and 429) and also miR-205 are being considered as new EMT markers considering their significant role during metastasis in almost all cancers by directly targeting expressions of Zeb1 and Zeb2 gene. The expression of CDH1 gene which transcribes E-cadherin, a key player in cell motility and cell invasiveness can be controlled by regulating expression of miR-9. In Glioblastoma cells, miR-10b regulates expression of HOXD10, RHOC, uPAR and MMP-14 genes hence regulating their role in invasiveness of tumor cells. Studies have shown that overexpression of miR-29b can cause reversal in EMT by inhibiting the invasive phenotype of tumor cells. A number of studies have shown that the downregulation of miR-138 can be linked with mesenchymal cell properties which lead to cell invasiveness during EMT. Liu *et al*., demonstrated that the downregulation of miR-138 also leads to reduced expression in E- cadherin and increased expressions of Vimentin as well [53].

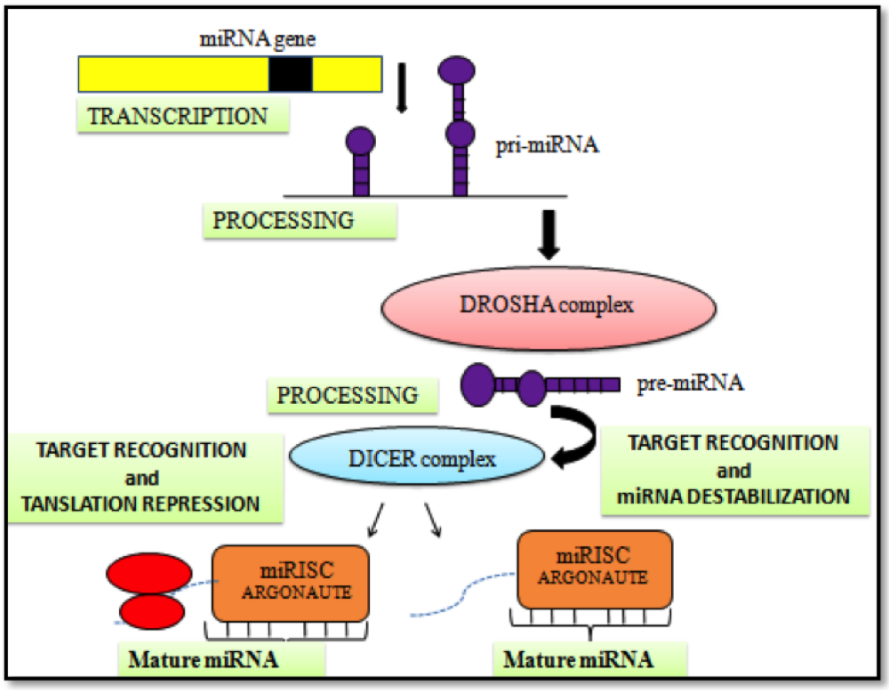

Figure 4: Biogenesis of miRNA: miRNA gene undergoes transcription to form Primary microRNA (pre-miRNA). This further undergoes nuclear cleavage processing to form Precursor microRNA (pre-miRNA). The pre-miRNA is cleaved in the cytoplasm to create microRNA duplex. This microRNA duplex unwinds and assembles into RISC (RNA Induced Silencing Complex) as mature miRNA. The mature miRNA then base pairs with mRNA and directs gene silencing).

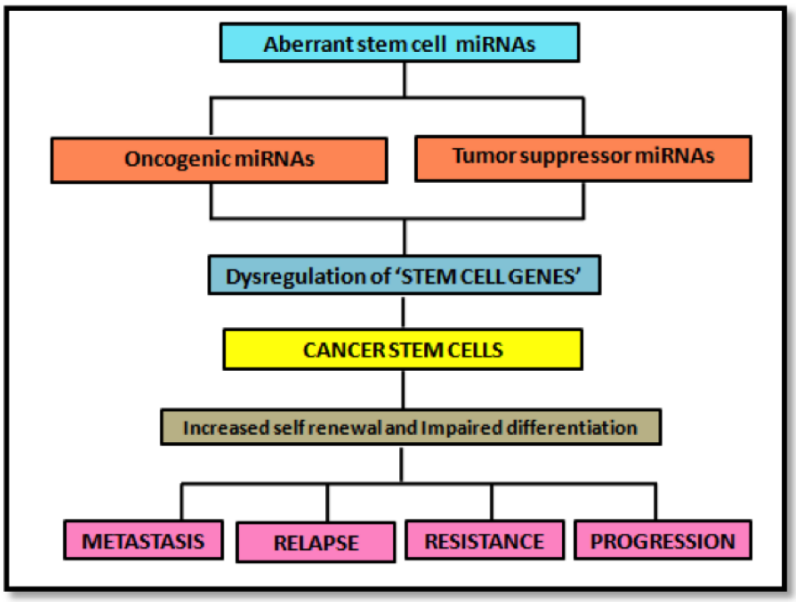

Figure 5: Relationship between miRNA and Cancer Stem Cells.

miR-200

The miR-200 family (miR-200a, miR-200b, miR-429, miR-200c, miR-141) potent inducer of epithelial differentiation and are generated from two transcripts, deriving from Chromosome 1 and 12 [54]. These tend to inhibit expression of ZEB 1 and ZEB 2 at post transcriptional level by binding to the target sites in their UTRs. Also, miR-200 family are transcriptional targets of ZEB1 and ZEB2. This leads to a double negative feedback loop known as ZEB/miR-200 feedback loop where activation of one group negatively affects the expression of other [55]. And thus, depending on extracellular signaling this loop switches and stabilizes epithelial or mesenchymal phenotype in Prostate cancer. Wang *et al.,* reported that miR-200

can directly regulate EMT and facilitate pluripotent stem cells by activating Oct4 and SOX2 [56].

miR-29b

miR-29b affects multiple steps during metastasis including invasion, motility, cellular survival and proliferation. Researchers have shown miR-29b in Prostate cancer cells inhibiting Mcl-1 and MMP2 protein expression [57]. Over expression of miR-29b induced reduced expressions of E-Cadherin and also reversal of EMT by expression of mesenchymal markers N-Cadherin, Twist and Snail and also the acquisition of a less invasive phenotype [58]. Thus, miR-29b plays a tumor suppressor role in Prostate cancer by inhibiting EMT and loss of miR-29b increases CD44+ stem cells levels during metastasis [59].

miR-34a

According to various studies sphere formation and tumor progression in Prostate cancer cells and in CD44+ cells can be inhibited by upregulation of miR-34 [60]. Hence, miR-34a can act as a therapeutic option for Prostate cancer with cancer origin of stem cells, being a critical negative regulator of Cancer Stem Cells.

miR-182 and miR-203

Overexpression of miR-182 and miR-203 have been shown to increase levels of E-cadherin/P-Cadherin and decrease SNAI2 expression therefore inducing significant mesenchymal to epithelial transition (MET) morphological characteristics. Thus MET can be induced in PC3 cells by re-expression of miR-182 and miR-203 [61]. Liu reported proliferation and invasion in PC3 cells by overexpression of miR-182 and downregulation of NDRG2 [62]. CD44 has been reported to maintain the stemness of CSCs by triggering SNAIL-mediated miR-203 suppression [63].

miR-320

miR-320 and β-Catenin expression is inversely correlated in CD44+ PCa cells. Furthermore, gene expression profiling of miR-320-overexpressing PCa cells showed a significant decrease in downstream target genes of the Wnt/β-Catenin pathway and CSC markers [64].

Let-7 family

The Let-7 family of miRNAs was first discovered in *Caenorhabditis elegans* and is seen to be functionally conserved in humans as well. In humans, 13-Let 7 family precursor miRNAs located on different nine chromosomes (Let-7a-1, Let-7a-, Let-7a-3, Let-7b, Let-7c, Let-7d, Let-7e, Let-7e, Let-7f, Let-7g, Let-7i, Let-98, Let-202) which are known to code for ten mature Let-7 miRNA isoforms [64]. The Let-7 family plays crucial role in controlling stem cell differentiation and its dysregulation results in a lesser differentiated cellular state leading to cancer [65].

Prostate CSCs were seen to have downregulated Let-7 expressions and with reconstitution of Let-7, growth of PC cells could be repressed [66]. The connection between EMT and let-7 is represented by the HMGA1 and HMGA2 genes, which are directly regulated by let-7 and were found to be implicated in EMT [67]. Further, miRNAs of the let-7 family were reported to directly, negatively regulate IL6, NRAS, c-Myc, HMGA1, HMGA2, and CCND2. The c-Myc protein regulates the biogenesis of let-7 by stimulating Lin28 which in turn blocks the maturation of let-7 [68]. Additionally, c-Myc stimulates the expression of HMGA1, AR, and IL6. HMGA2 on the influences HMGA1, its gene product in turn regulates the expression of c-Myc and HMGB1. HMGB1 was found to bind the AR promoter, AR protein was described itself to stimulate let-7 expression.

miR-30a

Downregulation of miR-30a-5p and 30c are seen to be a common scenario in variety of CD44+ cancer stem cell lines [69-71]. Integrin β3, the target gene of miR-30 is upregulated in various cancers [72]. ETS-related genes are the most frequently overexpressed oncogene in Prostate Cancer and a direct target of miR-30a. In his research Kao *et al*., showed that overexpression of miR-30a in PCa can inhibit cell migration and invasion hence suppressing EMT phenotype [73] thereby proving the role of miR-30a as a potential tumor suppressor in PCa. Similar results have been seen in other cancers as well, by targeting SNAIL and Vimentin. Overexpression of E-cadherin was observed in virtually all cases, and the majority of the mesenchymal markers, including N-cadherin, TGFB1, ZEB1, Vimentin, and SNAI2, were downregulated [74]. Also TWIST1 was overexpressed in majority of cases. This gene expression profile strongly suggests that localized PCa maintains the epithelial phenotype despite tumor differentiation and increasing stage.

miR-143 and miR-145

miR-143 and miR-145 have been seen to be crucial regulators during bone metastasis in Prostate cancer

Table 1: List of miRNAs and their Targets Implicated during Metastasis in Prostate Cancer

miRNAs	CSC markers	EMT markers
miR-143	CD133, CD44, Oct4, c-Myc, Klf-4, Sox2 [65]	Vimentin, Fibronectin, E-cadherin [66]
miR-34a	CD44+ [51]	Cyclin D1, CDK4, N-Myc, Snail [51]
miR-145	CD133, CD44, Oct4, c-Myc, Klf-4, Sox2 [65]	Vimentin, Fibronectin, E-cadherin [66]
miR-182	N-Myc, Nanog [52]	NDRG1 [53]
miR-203	CD44+ [52]	Snail [54]
miR-320	CD44+ [55]	Wnt/β-Catenin [55]
miR-708	CD44+ [67]	Akt-2 [67]
Let-7	CD44+, CD133+, c-Myc [56]	Ras, HMG, Bcl-2 [57-58]
miR-200b	Oct4, Nanog, Sox2 [47]	Zeb1, Zeb2, E-cadherin, Snail, Slug [45-46]
miR-373	CD44+ [68]	SIRT1, MMP9 [69-70]
miR-520c	CD44+ [68]	SIRT1, MMP9 [69-70]
miR-29b	CD44+ [50]	E-cadherin, N-cadherin, Twist, Snail [48-49]
miR-30a	Oct3, Integrin β1 [59-61]	Twist, Vimentin [63-64]

[75]. In a recently published report overexpression of both these miRNAs led to inhibition of cell viability and colony formation in Prostate cancer cells. Besides, decreasing tumor sphere formation, miR-143 and miR-145 suppress CSCs markers including CD133, c-Myc, Oct4, CD44 and Klf-4 in PC-3 cells [76].

miR-708

CD44 and CD133 expressing tumor initiating cells are known to be crucial contributors in tumor recurrence in Prostate cancer. Saini *et al*., reported that reduced miR-708 expression directly lead to repression of tumor initiation and progression by regulating CD44 and AKT2 [77].

miR-373 and miR-520c

These miRNAs are known to stimulate migration and invasion of cancer cells. Researchers report suppression of CD44 can explain the migration characteristics of miR-373 and miR-520c [78]. Both of these miRNAs exhibit dual action as oncogenes or tumor suppressor genes in different human cancers [79]. miR-373 and miR-520c contribute in metastasis by upregulating expressions of MMP-9 expressions by activating the Ras/Raf/Mek/Erk signaling pathways and directly targeting mTOR and SIRT1 [80-81].

CURRENT RESEARCH IN CANCER STEM CELLS REGULATING PATHWAYS

There is growing evidence that illustrates that many pathways classically connected with cancer may also be regulators of normal stem cell development. The pivotal signaling pathways of the “stem cell genes” viz. Notch, Hedgehog, Wnt/β-Catenin, etc are involved in the regulation of self-renewal, differentiation, and survival of cancer stem cells. These key signaling pathways, which may be deregulated in cancer stem cells, offer great promise for future cancer therapies and treatments.

The significant role of Wnt / β-Catenin pathway in promoting drug resistant properties in mixed lineage leukaemia (MLL) leukemic stem cells (LSCs) was first demonstrated by Yeung *et al*. Their work showed that by suppressing Wnt signaling in MLL, the leukemic stem cells could be brought back to the pre-MLL like stage which eventually would reduce growth of MLL Leukemic cells [82].

Similar results on Cancer stem cells were seen by regulating Hedgehog [83], Wnt [84] and Notch signaling [85-87] pathways in T-Cell Acute Lymphoblastic Leukemia (ALL), Chronic Myeloid Leukemia (CML), Medulloblastoma, Pancreatic Cancer [88] and Lung Adenocarcinoma [89]. Also, inhibition of Hedgehog signaling pathways may lead to reduction in clonogenic growth of CSCs in Multiple Myeloma, Colon Cancer [90], Myeloid Leukemia [91], Breast Cancer [92-93] and Multiple Myeloma [94].

FUTURE PERSPECTIVES

EMT has a crucial role in cancer radiation resistance and various studies have indicated that

induction of EMT enhances self-renewal and promotes acquisition of stem cell like characteristics which is further strengthened by expression of common markers such as Snail, Twist 1 and CD44 [95]. Karhadkar *et al.*, indicated that Hedgehog signaling pathway [96], Wnt signaling pathway [97], Notch signaling pathway [98], EGF receptor pathway [99] and p53 pathway [100] are among the main pathways targeting EMT and CSC maintenance in Prostate cancer [101]. Thus, any of the above pathways can be studied as indicators for carcinogenesis, and to facilitate pre-diagnosis of PCa which still remains a challenge.

Molecular miRNA therapy is very crucial for addressing oncogenesis linked with cancer stem cell dysregulation during EMT in castration resistant Prostate Cancer [102-103]. Hence, future researchers should focus on investigating miRNAs role in cancer stem cells self renewal pathways and also its potential role in early diagnosis and cancer progression, resistance and relapse.

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