Targeting Cancer Stem Cell-Related miRNAs for Prostate Cancer Therapy

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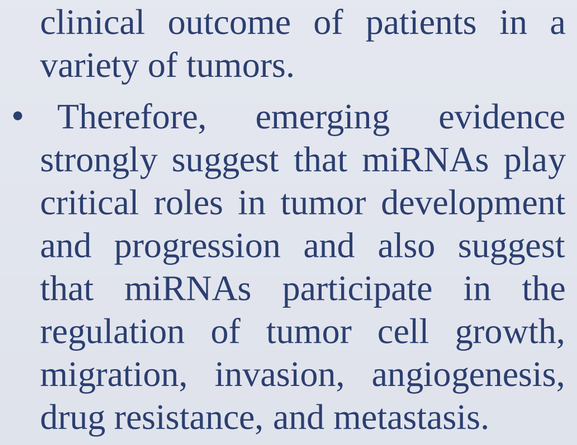
ABSTRACT

- Prostate cancer (PCa), a multifocal disease and one of the most commonly diagnosed cancers in the world. An important challenge in Prostate cancer therapy is the transition from androgen-sensitive to castration-resistant and metastatic prostate cancer.
- Recent evidences indicate that epithelial-to-mesenchymal transition (EMT) and cancer stem cells (CSCs) play crucial roles in the development of castration-resistance and metastasis of Prostate cancer. However, the regulation of CSCs and the involved signalling pathways during tumorigenesis are not well understood.
- MicroRNAs (miRNAs) are known to act as key regulators of the posttranscriptional regulation of genes, thus controlling a wide array of biological processes including tumorigenesis.
- The altered expressions of miRNAs have been associated with poor clinical outcome of patients in a variety of tumors.
- Therefore, emerging evidence strongly suggest that miRNAs play critical roles in tumor development and progression and also suggest that miRNAs participate in the regulation of tumor cell growth, migration, invasion, angiogenesis, drug resistance, and metastasis.
- Thus identification of signature miRNA associated with EMT and targeting CSCs-related miRNAs would likely lead to the inhibition of tumor growth thereby providing a novel therapeutic strategy for the treatment and/or prevention of Castration-Resistant Prostate cancer (CRPC) in the future.

Fig.1: Epithelial-Mesenchymal Transition



OBJECTIVES

- To identify CSCs and miRNA biomarkers of EMT in progressive Prostate cancer.
- To understand the signaling pathways being regulated by EMT markers during CRPC.

METHODOLOGY OF WORK

Literature Review :

- Pubmed , Google scholar, ISI websites were searched for research articles using keywords EMT, CSCs and Prostate Cancer.
- Identification of targets using miRTarbase.
- Signaling pathways associated with EMT and CSCs leading to CRPC using KEGG and PANTHER.

Literature survey for Prostate cancer Biomarkers

using PubMed, Google Scholar, ScienceDirect

Identification and segregation of specialised markers

Cancer stem cells (CSCs) | miRNA s

Identification of Targets in Epithelial-to-Mesenchymal Transition

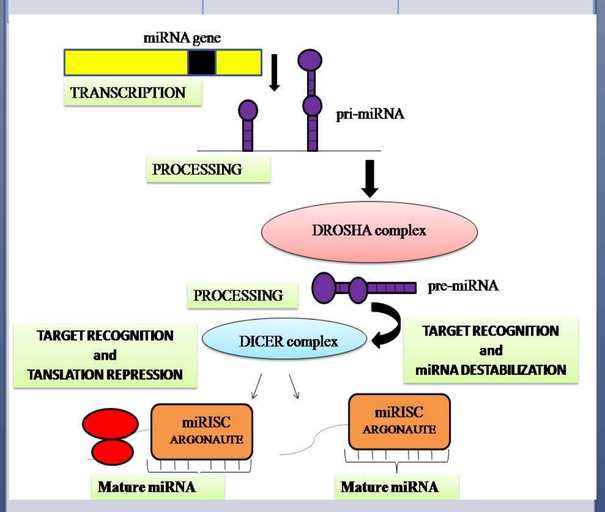
Literature Survey | miRTarbase

KEGG pathway database was used to find pathways for each of the identified targets

PANTHER database helped in functional classification of the targets in terms of molecular functions, biological process and protein class and their pathways.

RESULTS

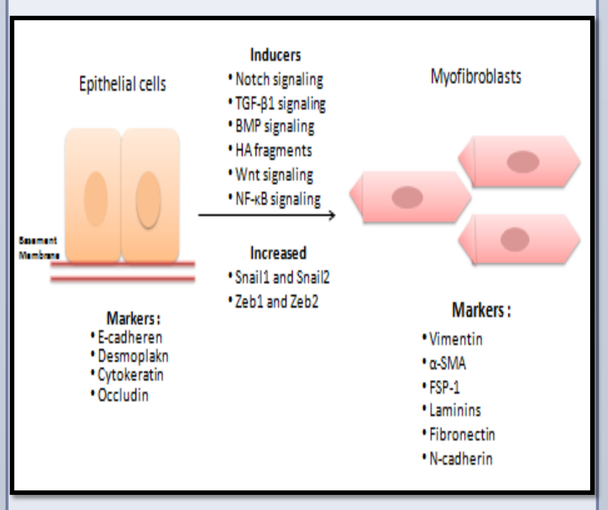
Cancer Stem Cell Markers	miRNA markers	miRNA markers
Nkx 3.1	miR-29b	miR-205
CD166	miR-15	miR-23b
NANOG	miR-107	miR-27b
Bmi-1	miR-145	miR-1
CD44+	miR-205	miR-203
P63	miR-143	miR-373
FNDC3B	miR-141	miR-520c
	miR-34a	miR-183
	miR-30	miR-9
	miR-200b	miR-182
	miR-200c	miR-320
	Let 7	miR-203



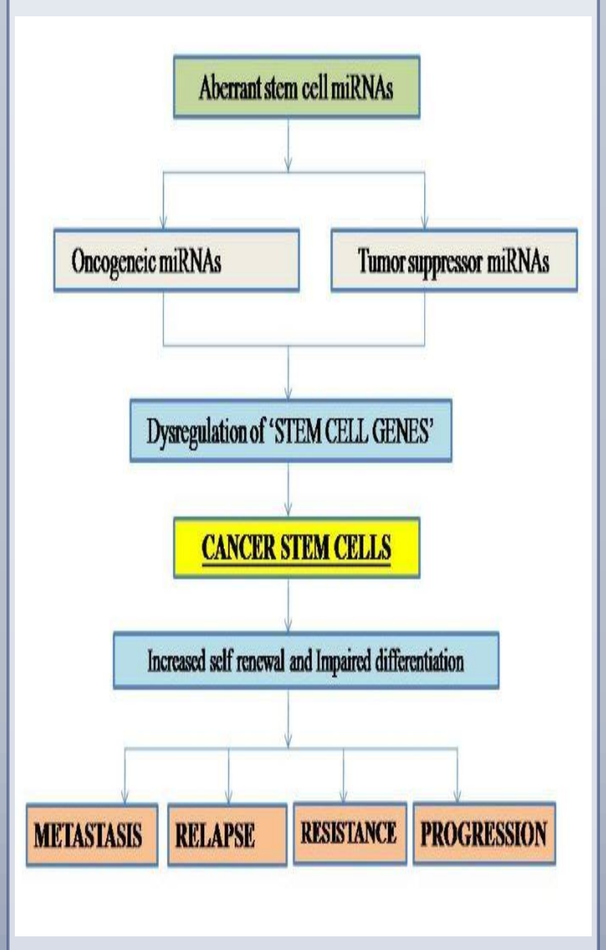
miRNA biogenesis

IDENTIFIED EMT MARKERS

N-Cadherin	TWIST	SNAIL1	SNAIL2
N-Chimaerin	ERBB3	PRKCI	E2F1
E2F5	ZEB2	ZEB1	NOTCH4
FOSL1	SIRT1	BCL2	MYCN
CD44	RAC1	LOX	MMP2
MMP9	VEGFA	TIMP-2	RUNX2
DKK3	SMAD4	EGR1	PTEN
Vimentin	Fibronectin	P63	FNDC3B
Granulin	SOX10	Occludin	MMP9

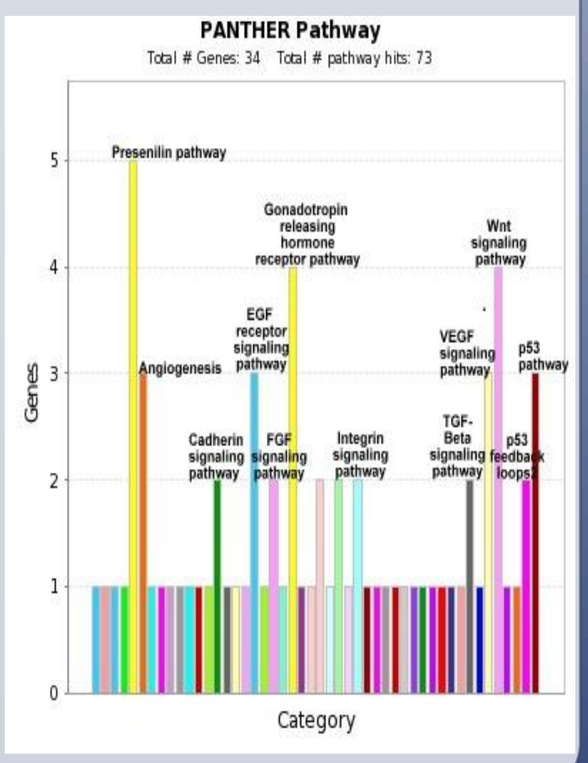


Biomarkers of EMT in Prostate cancer



Link between miRNAs and cancer stem cells

PANTHER ANALYSIS



CONCLUSIONS

- 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.
- Our studies indicated that **Gonadotropin releasing hormone receptor pathway, Wnt signaling pathway, Angiogenesis, EGF receptor pathway** and **p53 pathway** are among the main pathways targeting EMT and CSC maintenance in Prostate cancer.
- 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.

FUTURE PERSPECTIVES

- Molecular miRNA therapy is very crucial for addressing oncogenesis linked with cancer stem cell dysregulation during EMT in castration resistant Prostate Cancer. 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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