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Targeting LIN28: a new hope in prostate cancer theranostics

Garima Shrivastava[1], Alaa AA Aljabali[2], Seyed Hossein Shahcheraghi[3], Marzieh Lotfi[4], Madhur D Shastri[5], Shakti D Shukla[6], Dinesh K Chellappan[7], Niraj Kumar Jha[8], Krishnan Anand[9], Harish Dureja[10], Ritesh M Pabari[11], Vijay Mishra[12], Abdulmajeed G Almutary[13], Abdullah M Alnuqaydan[13], Nitin Charbe[14], Parteek Prasher[15], Poonam Negi[16], Rohit Goyal[16], Kamal Dua[17], Gaurav Gupta[18], Ángel Serrano-Aroca[19], Bojlul Bahar[20], Debmalya Barh[21], Pritam Kumar Panda[22], Kazuo Takayama[23], Kenneth Lundstrom[24], Paul McCarron[25], Hamid Bakshi[25] & Murtaza M Tambuwala*,[25]

[1]Department of Biochemical Engineering & Biotechnology, Indian Institute of Technology, Delhi, Hauz Khas, New Delhi, India
[2]Department of Pharmaceutics & Pharmaceutical Technology, Yarmouk University, Irbid-Jordan
[3]Infectious Diseases Research Center, Shahid Sadoughi Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[4]Abortion Research Centre, Reproductive Sciences Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[5]School of Pharmacy & Pharmacology, University of Tasmania, Hobart, Australia
[6]Priority Research Centre for Healthy Lungs, School of Medicine & Public Health, The University of Newcastle, Callaghan, Australia
[7]Department of Life Sciences, School of Pharmacy, International Medical University, Kuala Lumpur, Malaysia
[8]Department of Biotechnology, School of Engineering & Technology, Sharda University, Greater Noida, Uttar Pradesh, India
[9]Department of Chemical Pathology, School of Pathology, Faculty of Health Sciences & National Health Laboratory Service, University of the Free State, Bloemfontein, South Africa
[10]Department of Chemistry, School of Science, GITAM University, Hyderabad 502329, India
[11]RCSI, University of Medicine & Health Sciences, Dublin, Ireland
[12]School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India
[13]Department of Medical Biotechnology, College of Applied Medical Sciences, Qassim University, Saudi Arabia
[14]Department of Pharmaceutical Sciences, Rangel College of Pharmacy, Texas A&M University, Kingsville, TX 78363, USA
[15]Department of Chemistry, University of Petroleum & Energy Studies, Dehradun 248007, India
[16]School of Pharmaceutical Sciences, Shoolini University of Biotechnology & Management Sciences, Solan 173229, India
[17]Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Ultimo NSW 2007, Australia
[18]School of Pharmaceutical Sciences, Suresh Gyan Vihar University, Jaipur, India
[19]Biomaterials & Bioengineering Lab, Centro de Investigación Traslacional San Alberto Magno, Universidad Católica de Valencia, San Vicente Mártir, Valencia 46001, Spain
[20]International Institute of Nutritional Sciences & Food Safety Studies, University of Central Lancashire, Preston, United Kingdom
[21]Departamento de Genética, Ecologia e Evolução, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil
[22]Condensed Matter Theory Group, Materials Theory Division, Department of Physics & Astronomy, Uppsala University, Uppsala 75120, Sweden
[23]Center for IPS Cell Research & Application, Kyoto University, Kyoto 606-8397, Japan
[24]PanTherapeutics, Lutry CH1095, Switzerland
[25]School of Pharmacy & Pharmaceutical Sciences, Ulster University, Coleraine, County Londonderry, Northern Ireland BT52 1SA, UK
*Author for correspondence: m.tambuwala@ulster.ac.uk

The mortality and morbidity rates for prostate cancer have recently increased to alarming levels, rising higher than lung cancer. Due to a lack of drug targets and molecular probes, existing theranostic techniques are limited. Human LIN28A and its paralog LIN28B overexpression are associated with a number of tumors resulting in a remarkable increase in cancer aggression and poor prognoses. The current review aims to highlight recent work identifying the key roles of LIN28A and LIN28B in prostate cancer, and to instigate further preclinical and clinical research in this important area.

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Future Medicine

Prostate cancer (PCa) is one of the leading causes of cancer deaths in men worldwide [1,2], claiming over 350,000 lives annually [3]. Global cancer statistics for 2018 show that PCa is still the second-most frequent malignant cancer globally and there are estimated to be 2,293,818 new cases by 2040 [4]. Compared with many other cancer types, prostate cancer grows notoriously slowly, with a low cancer mortality rate [5]. When the cancer is localized within a specific organ, it is considered potentially curable but, sadly, cancer patients who develop castration-resistant cancers (CRPC) have a significantly decreased life expectancy [6,7]. The most prevalent diagnostics for PCa include prostate-specific antigen (PSA) testing, PCA3 urine testing, Prostate Health Index (PHI), the 4K test, MRI imaging, genomic analysis and MRI-transrectal ultrasound-guided (TRUS) prostate tissue biopsies. Treatment strategies include conventional chemotherapy, androgen-targeted agents and surgery, which is associated with tremendous pain and severe side effects [8,9]. Treatment also has limitations based on the age of the patient, preexisting health issues, site of tumor, and severity of cancer [10,11]. Hence, there is a dire need for an alternative, less painful, more accurate theranostic approach [12,13].

Serum PSA is a common biomarker for PCa (PSA>4 ng/ml). Its concentration fluctuates due to many factors such as malignancy and tumor recurrence, but is also found elevated in men with benign prostatic hyperplasia (BPH) and inflammation who are taking medication [14,15]. According to several reports, PCa diagnosis mainly relies on PSA-based tests. Although screening with PSA testing helps in early prostate cancer diagnosis (based on its level in blood and semen samples), it is not accurate and PSA levels have no effect on mortality from PCa [16,17]. For better diagnostic capability, new and more reliable biomarkers and probes are required. Targeting multiple biomarkers along with PSA may also increase the accuracy of detection of PCa.

LIN28 is an evolutionarily highly conserved RNA binding protein in higher eukaryotes. This protein acts as an oncogene associated with the regulation of several physiological functions, such as development, differentiation, insulin resistance and oncogenesis. It is reported to be an excellent biomarker under cancerous conditions of the prostate [18]. First discovered in *C. elegans,* the heterochronic gene LIN28 belongs to the highly conserved microRNA *let-7* family. The *let-7* family comprises 12 miRNA family members, playing critical roles as tumor suppressors [19]. *Let-7* binds to the 3′ end untranslated regions (UTRs) of key oncogenes including *Ras* and *Myc,* and inhibits their expression [20,21]. This is tightly regulated by RNA binding proteins such as LIN28A and LIN28B in higher eukaryotes [22]. Overexpression of human LIN28A and its paralog LIN28B are associated with a number of tumors resulting in remarkably increased cancer aggression and poor prognoses. After binding to precursor-*let-7* at its terminal loop, LIN28A adds Terminal Uridylyl Transferase (TUTase) that ultimately blocks microRNA biogenesis and tumor suppression [23,24]. LIN28A represses *let-7*-miRNAs (Figure 1), resulting in inhibition of the expression of *Ras*, *Myc*, and *HMGA2*-like oncogenes [25]. LIN28 is overexpressed in many cancers, making it a sensitive biomarker for a number of tumors, including PCa [26]. Several reports have suggested that this pathway's molecular targeting may increase theranostic sensitivity for a number of tumors. LIN28B, among innumerable downstream genes of *NF-κB* signaling pathway, has received great attention. It is a key oncogene and plays a role in blocking the biogenesis of *let7*-miRNA, which impedes various oncogenic target genes such as *Myc*, *Ras*, and *cyclins* (Figure 1) [27,28]. LIN28B can promote the development of neuroendocrine prostate cancer [29].

Early diagnosis of PCa is of the greatest concern, especially in metastases where tumor cells migrate from primary tissue to other organs, forming secondary tumors while resisting existing therapeutic agents. Moreover, PCa is a multiple-molecule-controlled disease. PSA, considered one of the most important and easily detectable antigen biomarkers in PCa patients, has been found notoriously imperfect as a diagnostic, leading to further unnecessary biopsies and painful investigations. Existing mono or combination therapies have shown very limited success in controlling cancer progression with a high reoccurrence rate and high mortality rate.

LIN28 and prostate cancer

LIN28 has been described as a regulator of developmental timing in *C. elegans* and an inhibitor of *let-7* pri-miRNA processing [30,31]. Moreover, *let-7c* miRNA has been described as a key regulator in androgen receptor (AR) expression and PCa targeting c-Myc. LIN28 overexpression and knockdown studies in an *in vitro* model of LNCaP and C4-2B cells and *in vivo* studies in a xenograft model highlighted the function of *let-7c* as a regulator of LIN28 in the progression and proliferation of PCa, and its inverse correlation with *let-7c*. The existence of a negative feedback loop of LIN28-*let-7c* was also confirmed in clinical specimens [32]. Downregulation of LIN28 increased *let-7c* expression and ultimately reduced AR expression and inhibited tumor growth [33]. These results suggest an interesting role for

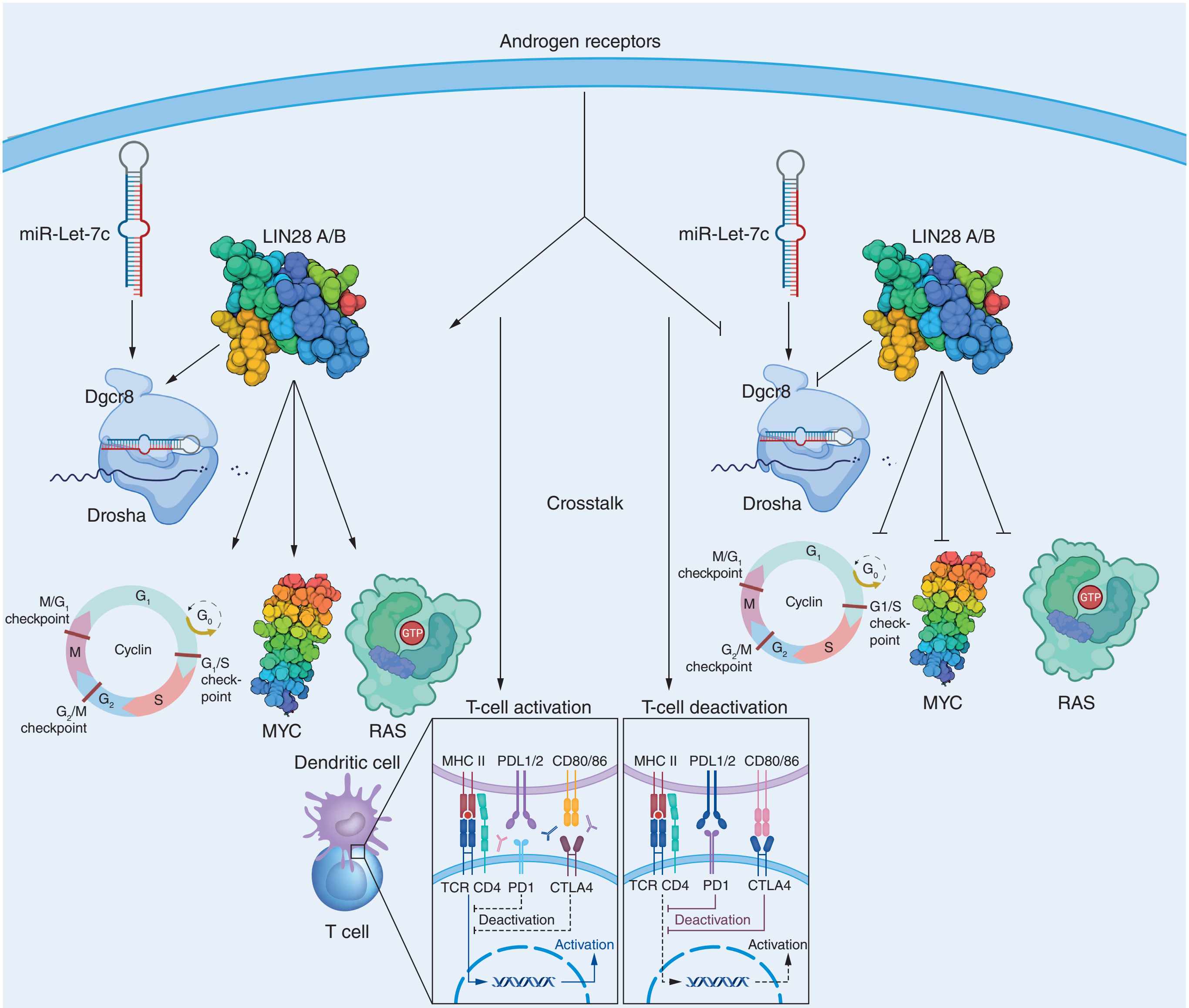

Figure 1. Crosstalk between LIN28 and miR-*let7* showing the inhibition of oncogenic target genes such as *Myc*, *Ras*, and *cyclins*.

LIN28 in PCa and the possibility of exploiting this pathway for therapeutic applications [32]. In another study, the down regulation of miRNA-*let-7c* in PCa, its correlation to cancer growth, and its potential as a tumor suppressor in the CRPC cell-line model were evaluated. Overexpression and downregulation of *let-7c* affected cell proliferation, anchorage-independent growth and clonogenicity contrarily in cell-line-based studies. Intratumoral administration of *let-7c* in a xenograft model reduced the tumor burden significantly. More importantly, gene expression studies in clinical samples confirmed the significantly increased expression of LIN28, a key regulator of miR-*let-7c* in *let-7c* downregulated samples, indicating a negative feedback loop between LIN28 and *let-7c,* and therapeutic potential for LIN28 in PCa treatment [34].

In an exciting study, a comparison of CRPC clinical samples with benign prostate tissue highlighted the role of LIN28. CRPCs are AR positive, and to determine the role of LIN28 in PCa progression, the authors analyzed human clinical Pca samples and were compared them with benign prostate tissue in several *in vitro* and xenograft models. Overexpression of LIN28 had a direct impact on PCa progression while downregulation of LIN28 resulted in reduced growth of PCa cells. Colony formation of CaP cells was also intensified irrespective of anchorage-dependent or -independent conditions. Injection of LNCaP cells stably expressing LIN28 in nude mice resulted in significantly higher tumorigenicity along with higher expression of AR and its targeting gene *NKX3.1*. *NKX3.1* functions as a negative regulator of epithelial growth in PCa. Moreover, prostate-specific antigen (PSA), a direct indicator of tumor angiogenesis and metastasis of prostate cancer, was observed [26].

A potential regulatory loop between LIN28B and miR-212 in androgen-independent PCa has also been reported [35]. LIN28B expression was found colocalized in the nucleus and cytoplasm of DU145 AIPC. Silencing of LIN28B resulted in increased c-Myc protein expression but downregulation of c-Myc mRNA in the same cell line. In DU145 cells, 19 miRNAs were found upregulated and 11 microRNA were downregulated. The miR-212 showed the highest upregulation, but TargetScan software-based analysis confirmed that c-Myc mRNA was not a potential target for miR-212. Instead, it was suggested that LIN28B: miR-212 may work as a regulatory loop in AIPC. LIN28B also showed unique miR binding characteristics compared with LIN28A, confirming a unique nucleotide binding feature for LIN28B [35].

Let7a, a marker and member of the LIN28-*let-7* miR axis, can act as both an oncogene and tumor suppressor [36]. It is dysregulated in several malignancies and is significantly downregulated in PCa patients. Furthermore, a panel of three miRNAs (miR-141, miR-145, and miR-155) was identified. Overall, *let7a* has shown superior diagnostic potential compared with PSA and digital rectal examination for the detection of PCa [36].

Development of resistance against second-generation antiandrogen enzalutamide or CYP17A1 inhibitor abiraterone has been documented [35]. To study the sensitivity of LNCaP cells to enzalutamide, arbiterone, or bicalutamide in comparison to control neo cells, different cell-based assays were performed, and results showed that LIN28 promotes the development of resistance to many targeted therapeutics such as enzalutamide, abiraterone, or bicalutamide by increasing expression of AR splice variants like AR-V7. LIN28 also plays a role in the upregulation of splicing factors such as hnRNP1 and may mediate the increased generation of AR splice variants in LIN28-expressing cells, thus confirming the importance of LIN28 in PCa progression [37].

Albino and colleagues found a new connection between the ETS transcription factor ESE3/EHF, LIN28-*let-7* miR axis and cancer stem cells (CSC) subpopulations [38]. CSCs are the most tumorigenic, metastatic and therapy-resistant class of cells in all types of tumors. The ETS transcription factor is directly associated with differentiation and development in many tissues, and its upregulation and downregulation render cells normal or oncogenic. In normal cells, the ESE3/EHF represses promoters for the LIN28A and LIN28B genes after binding to their promoters while activating transcription and maturation of *let-7* miR. In cancerous cells, the phenomenon was the opposite. The most noticeable finding was the critical association of cell transformation and expansion of prostate CSC with deregulation of the LIN28/*let-7* axis along with very low production of *let-7* miR. In cell lines and tumor xenografts, blocking the activity of LIN28A/LIN28B resulted in the loss of tumor initiation and self-renewal properties of prostate CSC. The results indicated that regulation via ETS homologs factor ESE3/EHF over LIN28/*let-7* axis was evident and acted as an obstacle to malignant transformation. The results also suggested different and novel therapeutic strategies to antagonize CSC in human PCa [38]. A list of reports highlighting the most important roles of LIN28 in prostate cancer is provided in Table 1.

Wang and colleagues used a fluorescence polarization assay to identify small-molecule inhibitors for both domains of LIN28 involved in *let-7* interactions. Results demonstrated selective pharmacologic inhibition of individual domains of LIN28 and provided a foundation for therapeutic inhibition of the *let-7* biogenesis pathway in LIN28-driven disease, especially in cancers [39]. Therapy-induced neuroendocrine prostate cancer (tNEPC) has become more prevalent due to increased utilization of antiandrogens to treat prostate adenocarcinoma (AdPC). Although the methods by which t-NEPC is established are unknown, new research indicate that AdPC cells can acquire an intermediate pluripotent stem cell (SC)-like phenotype that promotes the production of t-NEPCs. However, during the transition from AdPC to t-NEPC, it is uncertain if the core embryonic stem cell (ESC) genes (LIN28, POU5F1, SOX2 and NANOG) govern prostate cancer cells' stem-like state and the move from luminal epithelial to neuroendocrine lineage. According to Lovnicky and colleagues, LIN28B plays a vital role in the transition from AdPC to t-NEPC, and the overexpression of LIN28B may enhance proliferation and transdifferentiation, which may aid int-NEPC development [40]. They discovered that nearly half of t-NEPC patient tumors gained LIN28B and SOX2 expression by comparing published RNA-seq data. Using t-NEPC cell and xenograft models, standard molecular and cellular biology approaches were used to investigate the activities of LIN28B and its interaction with SOX2. They found a positive correlation between LIN28B and SOX2 mRNA levels in a variety of cell types, transgenic mice, patient-derived xenografts and patient malignancies [40]. Immunohistochemistry-based analysis indicated that LIN28B and SOX2 expression were co-upregulated in a group of t-NEPC patients.

Table 1. LIN28's most important roles in prostate cancer.

Published research	Role of LIN28	Ref.
Moss *et al.* 1997 and Morita and Han, 2006	Inhibitor of *let*-7 pri-miRNA processing	[30,31]
Nadiminty *et al.* 2012	Progression and proliferation of PCa and its inverse correlation with *let-7c* Downregulation of LIN28 increased *let-7c* expression and ultimately reduced AR expression, inhibited tumor growth	[32]
Nadiminty *et al.* 2012	miR-*let-7c* as a potential tumor suppressor in CRPC cell-line model. Overexpression and downregulation of *let-7c* affected cell proliferation, anchorage-independent growth and clonogenicity in opposite manner in cell-line-based studies	[34]
Tummala *et al.* 2013	Overexpression of LIN28 has direct impact on PCa progression while downregulation of LIN28 resulted in reduced growth of PCa cells	[26]
Borrego-Diaz *et al.* 2014	miR-212 may work as regulatory loop in AIPC; LIN28B shows unique miR binding characteristics compared with LIN28A, confirming a unique nucleotide binding feature for LIN28B	[35]
Tummala *et al.*, 2016	LIN28 plays a role in upregulation of splicing factors, such as hnRNP1, and may mediate the increased generation of AR splice variants in LIN28-expressing cells	[37]
Albino *et al.*, 2016	ESE3/EHF activated promoters for LIN28A and LIN28B genes after binding to its promoters while repressing transcription and maturation of *let-7* miRNA	[38]
Lovnicky *et al.*, 2019	LIN28B plays a key role in the transition from AdPC to t-NEPC, and overexpression of LIN28B may promote proliferation and transdifferentiation, which may contribute to t-NEPC progression	[40]
Chen *et al.*, 2019	LIN28 promotes PD-L1 expression	[21]

AdPC: Prostate adenocarcinoma; AR: Androgen receptor; CRPC: Castration-resistant cancer; PCa: Prostate cancer; tNEPC: Therapy-induced neuroendocrine prostate cancer.

DuNE xenograft initiation and tumor growth were decreased by CRISPR gene deletion of the LIN28B gene. The inhibitory actions of LIN28B on miRNA *let-7d* led in the upregulation of HMGA2- and HGMA2-mediated SOX2 transcription. Overall, the LIN28B/*let-7*/SOX2 axis has been validated as a key signaling mechanism that controls a cancer stem-like phenotype [40].

Chen and colleagues discovered that miRNA *let-7* reduces the expression of PD-L1 – a type I transmembrane protein that interacts with the T-cell inhibitory receptor PD-1 – and is thought to be an immune-checkpoint-protein expression [21]. *Let-7* biogenesis is inhibited by LIN28, which promotes PD-L1 expression. As a result, inhibiting LIN28 could be an approach to preventing cancer cells from evading the immune system. Treatment with LIN28 inhibitors also raises *let-7* and reduces PD-L1 expression, leading to antitumor immunity reactivation *in vitro* and *in vivo* [21].

Discussion

Prostate cancer is the most prevalent nonskin cancer in men and is one of the leading cause of cancer-related death [41]. LIN28, a member of the LIN28/*let-7*/*Myc* axis, is overexpressed in PCa, activates AR and promotes the growth of PCa cells; therefore, LIN28 has a novel role in PCa development [26]. This factor has key roles, including inhibiting *let*-7 pri-miRNA processing [30,31], tumor progression and proliferation, effectiveness on AR expression [32,33], c-Myc protein expression (32, 35), development of resistance to many targeted therapeutics, increasing expression of AR splice variants like AR-V7 [37] and, finally, cell transformation and expansion of prostate CSC in PCa [38]. The current review also confirms the importance of LIN28 in prostate progression. The findings described underline the multifactorial nature of LIN28 and present it as an attractive target for therapeutic intervention in PCa.

Future perspective

Despite a huge number of publications, information about the function of LIN28 in PCa is consistent, yet limited. The current findings should stimulate further preclinical and clinical research targeting LIN28 as a potential pharmacological target in developing novel therapeutics for the effective management and treatment of PCa patients. This could reduce the mortality associated with PCa and greatly improve the quality of life of men affected by prostate cancer. However, during tumor progression, whether the function of such genes is downregulated accordingly is a critical question in miRNA biology and holds value for future research. Several published studies have emphasized the importance of LIN28 as a target for chemotherapy, especially in patients with a subset of cancers with poor prognosis. With more sophisticated and high-throughput tools to study the role of small molecules, the future of LIN28 research is promising for preclinical drug development. Future studies should be directed toward revealing the precise role of LIN28 in not just prostate cancer, but other types of cancers and several other diseases. This should, in turn, promote research on LIN28-based cancer therapeutics and theranostics.

Summary points

- Prostate cancer is the leading cause of cancer-related deaths worldwide among men.
- Downregulation of LIN28 increased tumor growth.
- Overexpression of LIN28 halts PCa progression.
- LIN28B shows unique miR binding characteristics in contrast with LIN28A, confirming a unique nucleotide binding feature for LIN28B.
- LIN28B/*let-7*/SOX2 axis is a critical signaling pathway for the regulation of cancer stem-like phenotype for the promotion of t-NEPC.
- Pharmacologic inhibition of individual domains of LIN28 provides a foundation for therapeutic inhibition of the *let-7* biogenesis pathway in LIN28-driven disease, especially cancers.

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