REVIEW

PRNCR1: a long non-coding RNA with a pivotal oncogenic role in cancer

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Abstract

Long non-coding RNAs (lncRNAs) have been gaining importance in the field of cancer research in recent years. *PRNCR1* (*prostate cancer-associated non-coding RNA1*) is a 12.7 kb, intron-less lncRNA found to play an oncogenic role in malignancy of diverse organs including prostate, breast, lung, oral cavity, colon and rectum. Single-nucleotide polymorphisms (SNPs) of *PRNCR1* locus have been found to be associated with cancer susceptibility in different populations. In this review, an attempt has been made for the first time to summarize all sorts of available data on *PRNCR1* to date from relevant databases (GeneCard, LncExpDB, Ensembl genome browser, and PubMed). As functional roles of *PRNCR1*, miRNA (microRNA) sponging was mostly highlighted in the pathogenesis of different cancer; in addition, an association of the lncRNA with chromatin-modifying complex to enhance androgen receptor-mediated gene transcription was reported in prostate cancer. Diagnostic and prognostic importance of *PRNCR1* was found in some malignancies suggesting potency of the lncRNA to serve as a clinical biomarker. For *PRNCR1* SNPs, although cancer susceptibility of the risk alleles/genotypes was reported in different populations, majorities of the findings were not replicated and underlying molecular mechanisms remained unexplored. Therapeutic implication of *PRNCR1* was not studied well and future research may come up in this direction for intervening novel strategies to fight against cancer.

Introduction

Recent advances in RNA-seq data analysis reveal that around 80–85% of the human genome is actively transcribed and majority of the transcripts are non-coding RNAs (ncRNAs) (Djebali et al. 2012; Hangauer et al. 2013). Long non-coding RNAs (lncRNAs) have a standard length of > 200 nucleotides (Adhikary et al. 2019) and are similar to mRNAs in many aspects, i.e., lncRNAs like mRNAs are transcribed by RNA polymerase-II, have exon structures interrupted by introns, undergo post-transcriptional modifications like 5'capping, 3'polyadenylation, splicing and exhibit cell-type-specific, tissue-specific and developmental stage-specific expression patterns (Chernikova et al. 2016; Sun et al. 2018; Liu et al. 2016; Derrien et al. 2012; Sarropoulos et al. 2019). LncRNAs also serve as vital regulators of gene expression by modulating processes like transcription, splicing, mRNA turnover, and translation (Faust et al. 2012; He et al. 2019; Martone et al. 2020). Association of lncRNAs with disease conditions including cancer has been established and, oncogenic and tumor-suppressive lncRNAs have been designated in human malignancies (He et al. 2019). Therefore, genes encoding lncRNAs should be studied with equal priority to that of protein-coding genes for exploring molecular pathogenesis of associated disease conditions.

Prostate cancer-associated non-coding RNA1 (*PRNCR1*) is an intron-less lncRNA known to play oncogenic role in prostate cancer (Chung et al. 2011). The role of *PRNCR1* has also been reported in the malignancy of other organs (Pang et al. 2019; Cheng et al. 2018) and in addition, single-nucleotide polymorphisms (SNPs) of the gene have been found to be associated with cancer susceptibilities (Sattarifard et al. 2017; Li et al. 2013, 2016a). Thus, *PRNCR1* seems to be an important lncRNA to be explored in more detail in different aspects of human malignancy and for this, a review work summarizing the available data will be helpful which

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is lacking altogether to the best of our knowledge. On the aforesaid backdrop, the present study attempts to summarize available information of *PRNCR1* from published literature with special emphasis on its role in the pathogenesis of human cancers and its potential diagnostic, prognostic, as well as therapeutic values for associated disease conditions.

Genomic locus and biogenesis

PRNCR1 is localized in chromosomal 8q24.21 region (GRCh38/hg38) which is a part of 8q24 gene desert of human genome (Chung et al. 2011; Huppi et al. 2012). Besides *PRNCR1*, 8q24 also contains other lncRNA genes like *prostate cancer-associated transcript 1* (*PCAT1*), *cancer-associated region long non-coding RNA-5* (*CARLo-5*), *plasmacytoma variant translocation-1* (*PVT1*), etc. and protein-coding genes like *POU Class 5 Homeobox 1B* (*POU5F1B*) and *MYC* (Huppi et al. 2012; Kim et al. 2014). Chromosome 8q24 was found to undergo frequent genetic alterations like amplification, deletion, translocation and viral-integration in different cancers (Huppi et al. 2012). In cervical cancer, the 8q24.21 region harboring *PRNCR1* locus was reported as a preferred site for

integration of the human papillomavirus (HPV) genome (Bodelon et al, 2016). *PRNCR1* gene is intron-less, consists of a single exon of approximately 12.7 kb and occupies a position overlapping with *PCAT1* locus in a sense direction (GRCh38.p13) (Fig. 1). In addition to *PRNCR1*, *CARLo-5* and *POU5F1B* loci also overlap with *PCAT1* locus in antisense and sense directions, respectively. Total 4 transcript variants of *PRNCR1* have been reported with following transcript IDs; URS00009C6066_9606 (12,727 nucleotides), URS0000759F81_9606 (12,722 nucleotides), URS0000E9A964_9606 (12,722 nucleotides) and URS-0001BCD7EB_9606 (12,721 nucleotides) (GeneCards, http://www.genecards.org). In addition to minute difference in length, *PRNCR1* transcripts show variation at 5' and 3' end sequences. *PRNCR1* promoter is not well defined although the gene locus has five enhancer elements having binding sites for transcription factors (GeneCards, http://www.genecards.org). Thus, transcriptional regulation of *PRNCR1* is not well characterized. However, the chromosomal 8q24 region harbors *MYC* super-enhancer elements that involve long-range transcriptional regulation of the host gene as well as of adjacent loci (Lancho and Herranz 2018). Long-range physical interaction of *MYC* enhancer was
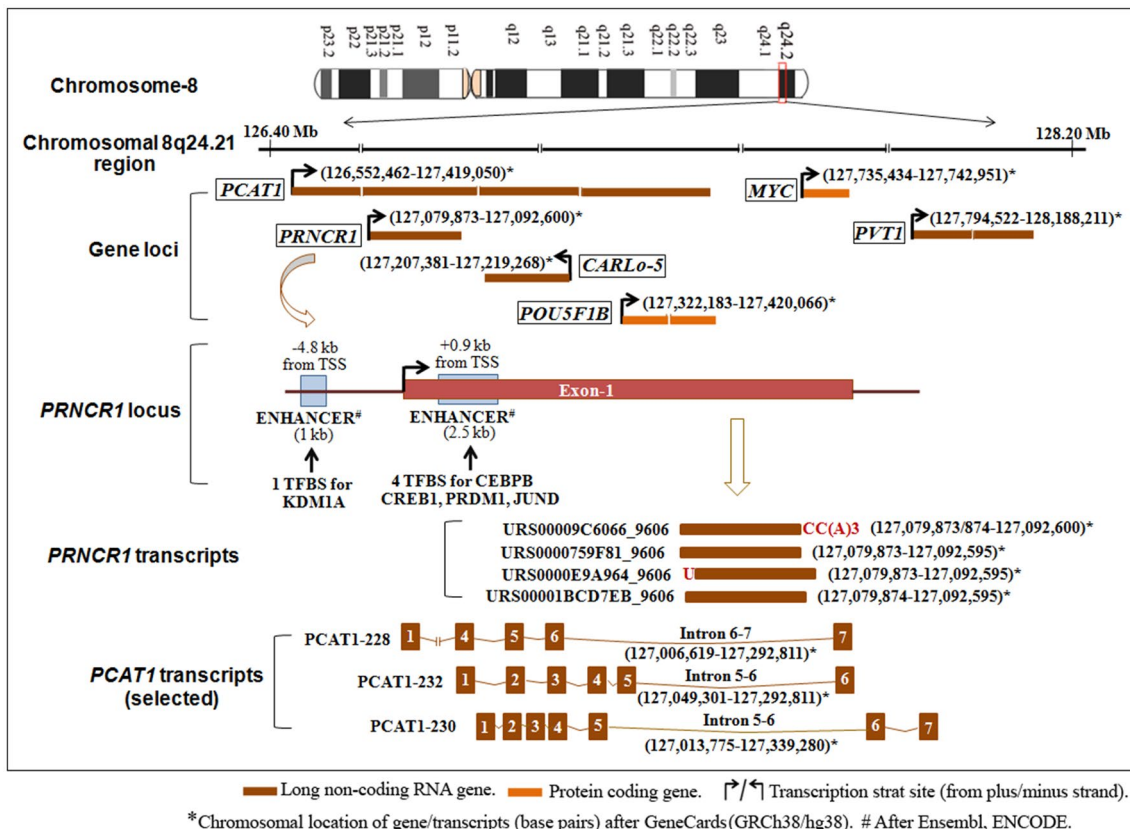

Fig. 1 Schematic view of human chromosomal 8 q24.21 region harboring *PCAT/PRNCR1* locus and adjacent genes loci. Exons are represented as boxes and introns as connecting lines in transcripts. *TSS* transcription start site, *TFBS* transcription factor binding site

established with the promoter of *CARLo-5* locus leading to transcriptional up-regulation of the latter (Kim et al. 2014); such probability for transcriptional regulation of *PRNCR1* has not been tested in any investigation to date.

Gene expression profile under normal and diseased conditions

Expression profile of *PRNCR1* in normal body tissue of adult and developmental stages in human was downloaded from LncExpDB (https://bigd.big.ac.cn/lncexpdb) (Li et al. 2021a). *PRNCR1* is expressed about ubiquitously in majority of organs of human body (Fig. 2A) (Project ID, E-MTAB-2836; source, EBI ArrayExpress), suggesting importance of the lncRNA in normal physiological functioning. In addition to endometrium, prostate and appendix, comparatively higher *PRNCR1* level was also found in spleen and lymph node than other organs; this indicated an association of the lncRNA in host's immune response which was also evident from its (*PRNCR1*) differential expression pattern in peripheral blood lymphocyte in response to HIV, HCV, HBV infections (GSE125686), and in primary lung epithelium in response to SARS-CoV-2 infection

(GSE147507) compared to normal control (Fig. 2B). However, functional link of *PRNCR1* with host's immunity is not explored to date, although role of the lncRNA has been reported in activation of androgen receptor which is also expressed in immune cells and involved in development and regulation of innate as well as adaptive immune responses (Yang et al. 2013; Lai et al. 2012). Furthermore, a significant association of the *PRNCR1* variant (rs1456315) with the susceptibility of osteoarthritis, an immune response related disease was also found in a Chinese population (Wang et al. 2018).

During organogenesis, *PRNCR1* level increased substantially in the embryonic cerebellum on the 10th week and in the embryonic heart between 9th and 13th weeks of gestation (Fig. 2C) (Project ID, E-MTAB-6814; source, EBI ArrayExpress) functional significance of which was not investigated. But, *PRNCR1* through miRNA sponging was found to up-regulate the expression of HEY2 and CCND2 (Cheng et al. 2018; Ouyang et al. 2021) that were also reported to have involvement in the development of embryonic heart and cerebellum, respectively (Anderson et al. 2018; Leto et al. 2011). However, lncRNAs generally show cell type-specific expression patterns in tissue in connection
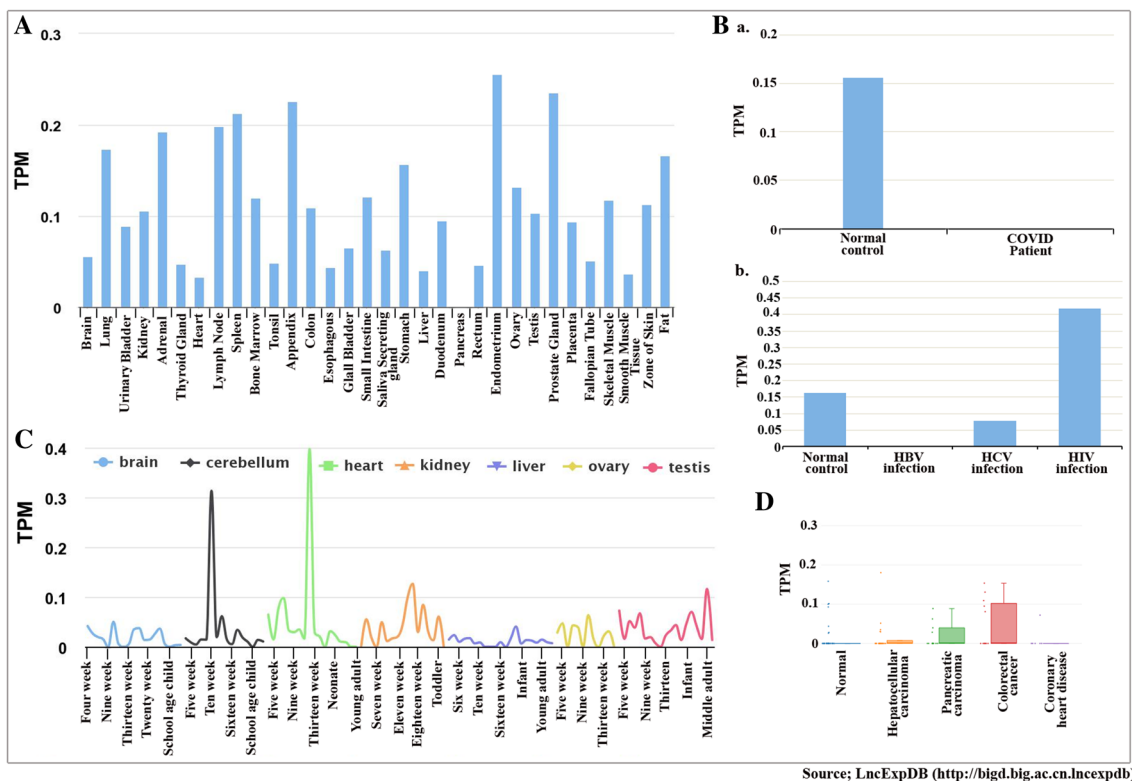

Source; LncExpDB (http://bigd.big.ac.cn.lncexpdb)

Fig. 2 Summarized view on expression pattern of *PRNCR1* in human body. *PRNCR1* expression levels in normal tissue of different organs (**A**), in blood samples of normal and virus infected individuals (**B**), during development of 7 vital organ from early organogenesis to adulthood (**C**) and in blood exosomes of normal and diseased individuals (**D**). *TPM* transcript per million, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus

to their specific biological function, i.e., *LOC646329* was abundantly expressed in human radial glia cells but, a low overall expression level of the lncRNA was found in the neocortex tissue (Liu et al. 2016). Therefore in *PRNCR1*, detailed information on the expression pattern is warranted up to the cell type level in adult and embryonic tissues for more precise functional interpretation.

Apart from the body tissue/organ, *PRNCR1* expression was also detected in blood exosomes of normal and diseased individuals (GSE100063, GSE100206) (Fig. 2D) and the phenomenon may have association with cell-to-cell communication process in endocrine manner.

Among diseased conditions, *PRNCR1* was mostly studied in association with cancer and frequent over-expression of the lncRNA was found in malignant tumors of prostate (Chung et al. 2011), breast (Pang et al. 2019), oral cavity (Liu et al. 2021), etc. Molecular mechanisms associated with *PRNCR1* over-expression remained unexplored; however, frequent amplification of the chromosomal 8q24.21 region harboring *PRNCR1* locus in different malignancies (Raeder et al. 2013; Bhosale et al. 2017) might be a probable explanation. Furthermore, transcription factors like KDM1A, JUND, CEBPB and CREB1 having binding sites on *PRNCR1* enhancer elements (Fig. 1) were over-expressed in malignant conditions (Kashyap et al. 2013; Elliott et al. 2019; Milde-Langosch et al. 2003; Fang et al, 2016) and hence might contribute significantly to the transcriptional up-regulation of the lncRNA gene.

Functional role of *PRNCR1* in oncogenesis

Oncogenic impact of *PRNCR1* was evident from its influence on dysregulation of vital cellular processes like epithelial–mesenchymal transition, proliferation, migration and so on in different human malignancies (Table 1). As potential mechanism of *PRNCR1*-mediated oncogenesis, androgen receptor (AR) regulated gene activation, modulation of key regulatory proteins of cell cycle progression and sponging of miRNA targeting mRNA of oncogenic function were mostly highlighted (Table 1, Fig. 3). So far, the interaction of five miRNAs with *PRNCR1* was established experimentally in different human malignancies; *PRNCR1* is found to harbor four binding sites for miR-326, three sites for miR-944, and one site each for miR-126-5p, miR-377, and miR-448 that (binding sites) remain scattered roughly along the length of the lncRNA (Fig. 3A).

Table 1 Summarized information on oncogenic role of *PRNCR1* in different cancer

Disease (cancer)	Molecular alteration	Functional role	Molecular target (probable mechanism)	Downstream oncogenic impact	Clinical importance	References
Prostate cancer	Over expression	Proliferation (↑)	AR (interaction and recruitment of chromatin-modifying complex)	Aberrant AR activation	N/A	Yang et al. (2013)
Breast cancer	Over expression	Proliferation (↑) Migration (↑) Invasion (↑) EMT (↑) Apoptosis (↓)	i. CHK1/2 & AKT (modulation of phosphorylation state) ii. miR-377 (sponging)	i. CHK1/2 inactivation and AKT activation ii. CCND2 over-expression	Diagnostic Prognostic Therapeutic	Abdollahzadeh et al. (2020); Guo et al. (2019); Ouyang et al. (2021); Pang et al, (2019)
NSCLC	Over expression	Proliferation (↑) Migration (↑) Invasion (↑) EMT (↑) Apoptosis (↓)	i. miR-488 (sponging) ii. miR-126-5p (sponging)	i. HEY2 over-expression ii. MTDH over-expression	N/A	Cheng et al. (2018); Guo et al. (2020)
OSCC	Over expression	Proliferation (↑) Migration (↑) Invasion (↑) Apoptosis (↓)	i. miR-944 (sponging) ii. miR-326 (sponging)	i. HOXB5 over-expression ii. FSCN-1 over-expression	Prognostic	Lin et al. (2020); Liu et al. (2021)
Colorectal cancer	Over expression	Proliferation (↑) Migration (–) Invasion (–) apoptosis (–)	N/A	N/A	Diagnostic Prognostic	Yang et al. (2016)

NSCLC non-small cell lung carcinoma; *OSSCC* oral squamous cell carcinoma; EMT epithelial-to-mesenchymal transition

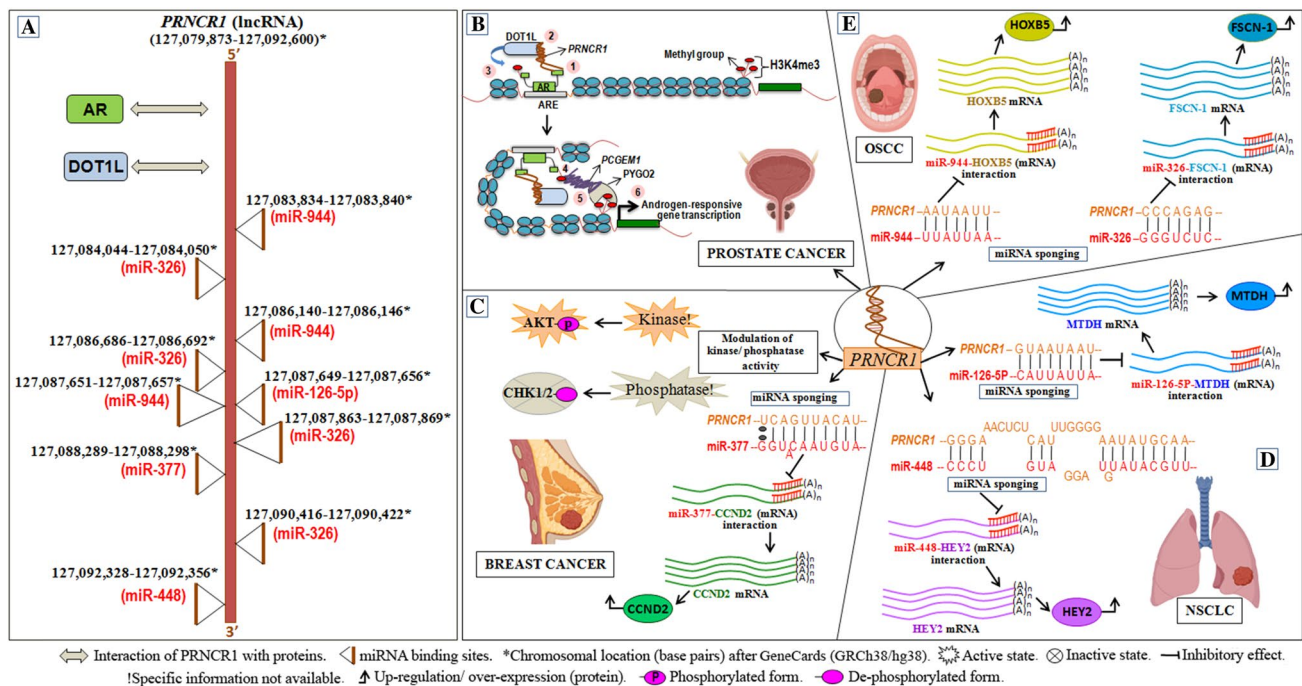↑: positive impact; ↓: negative impact; –: no effect; N/A: data not available

Fig. 3 Summarized information on functional mechanism of *PRNCR1* in oncogenesis. **A** Schematic view showing interaction *PRNCR1* with proteins and target miRNAs. **B–D** details of *PRNCR1*-mediated oncogenesis in prostate cancer, breast cancer, non-small cell lung carcinoma (NSCLC) and oral squamous cell carcinoma (OSCC). 1–6; *PRNCR1*-mediated expression of androgen responsive genes through chromatin modification via recruitment of DOT1L (DOT1-Like Histone Lysine Methyltransferase), *PCGEM1* (Prostate Cancer Gene Expression Marker 1, an lncRNA) and PYGO2 (Pygopus Homolog). *AR* androgen receptor, *ARE* androgen response element, *H3K4me3* trimethylation at 4th lysine residue of H3 histone. The cartoon symbols for the malignancies have been created with BioRender. com

Prostate cancer

PRNCR1 transcript was first cloned and characterized successfully as lncRNA in human prostate tissue and prostate cancer cell line (Chung et al. 2011). The investigators found *PRNCR1* over-expression in prostate cancer (PCa) cells and prostatic intraepithelial neoplasia; furthermore, reduced PCa cell viability and simultaneously decreased androgen receptor (AR) trans-activation following knockdown of *PRNCR1* strongly suggested its association in AR signaling pathway. In PCa, AR is aberrantly activated and serves as a master regulator for G1–S progression of cell cycle through inactivation of retinoblastoma protein, promoting G1 cyclin-dependent kinase activity, etc. (Balk and Knudsen 2008). According to Yang et al., *PRNCR1* over-expression in prostate cancer causes significant enhancement of ligand-dependent and ligand-independent AR activation (Yang et al. 2013). From experimental evidences, the authors propose that *PRNCR1* interacts with AR bound to androgen response element (ARE) and mediates its (AR) methylation via recruitment of DOT1-like histone H3K79 methyltransferase (DOT1L); *prostate cancer gene expression marker 1* (*PCGEM1*, a lncRNA) binds to methylated AR and recruits pygopus family PHD finger 2 (PYGO2) which recognizes

active chromatin mark (H3K4me3) leading to selective looping of AR-bound enhancer (ARE) with promoter of the target gene and its transcriptional activation (Fig. 3B). The authors also highlighted importance of *PRNCR1* in ligand-independent aberrant activation of full length and truncated AR in castration resistant prostate cancer (CRPC); following sh-RNA mediated knock-down of *PRNCR1* and also *PCGEM1*, they found reduced growth of CRPC cells in tumor xenograft. On contrary, Prensner et al. did not find any evidence for *PRNCR1* to interact with AR in prostate cancer and therefore failed to establish this lncRNA as a component of AR signaling pathway (Prensner et al. 2014). The discrepancies might be due to differences in prostatic lesions used with respect to tumor stage, Gleason scores, ethnicity of the patients, etc. and methodological details employed by the investigators (Yang et al. 2013 and Prensner et al. 2014).

Breast cancer

In breast cancer (BC), consistent over-expression of *PRNCR1* was found in primary breast tumor compared to adjacent normal tissue (Pang et al. 2019; Abdollahzadeh et al. 2020; Guo et al. 2019; Ouyang et al. 2021). *PRNCR1* knockdown led to apoptosis induction and suppression of

tumor associated phenotypes like proliferation, migration, invasion and epithelial to mesenchymal transition in BC cells (Pang et al. 2019). As molecular mechanism of tumorigenesis, the role of *PRNCR1* in modulating functional state or expression level of some key cell cycle regulator proteins was highlighted. From the evidence of knockdown experiment in BC cell line, *PRNCR1* was predicted to involve in maintenance of CHK1/2 proteins in dephosphorylated and AKT in phosphorylated forms, and thus keeping the former in inactive and the latter in active states to augment cell cycle progression (Fig. 3C). However, the candidate phosphatase and kinase serving as functional mediators of *PRNCR1* activity need to be identified for better understanding of the disease pathogenesis. Very recently in BC cell line, *PRNCR1* was found to bind with miR-377 competitively and up-regulate the expression of its (miRNA) natural target CCND2 (Ouyang et al. 2021); CCND2 over-expression was also correlated with aberrant activation of MEK/MAPK pathway leading to accelerated cell cycle progression and suppression of apoptosis in BC cells, and thus was speculated to contribute to the breast tumor growth. On the contrary, significantly reduced expression of CCND2 was frequently reported in primary breast tumors compared to adjacent normal tissue and promoter hyper-methylation was highlighted as a potential mechanism of gene inactivation (Fischer et al. 2002; Evron et al. 2001; Truong et al. 2015). Moreover, in another study dealing with the TCGA dataset, promoter hyper-methylation of *CCND2* and associated reduced gene expression in breast tumor was found to be associated with poor patient prognosis (Hung et al. 2018). Therefore, in breast cancer, the role of CCND2 as a downstream oncogenic effector of *PRNCR1* seems to be a matter of scientific debate and the findings (Ouyang et al. 2021) of in vitro experimental system that lacks tumor micro-environment altogether needs to be replicated in primary breast tumors for the validation purpose.

Non-small cell lung cancer

Non-small cell lung cancer (NSCLC) accounts for more than 80% of lung cancer (Ettinger et al. 2012). In NSCLC, *PRNCR1* was found to act as competitive endogenous RNA (ceRNA) for mir-126-5p and mir-448 (Fig. 3D) (Guo et al. 2020; Cheng et al. 2018). Experimental evidences showed that mir-126-5p and mir-448 inhibited cell proliferation, migration, invasion and epithelial to mesenchymal transition (EMT) in NSCLC through attenuating MTDH (metadherin) and HEY2 (Hairy and enhancer of split-related with YRPW motif protein 2) mRNAs, respectively. MTDH is a cell adhesion molecule frequently over-expressed in primary NSCLC tumors (Zhang et al. 2018; Guo et al. 2020). Oncogenic impact of MTDH may be exerted through several signaling pathways like Wnt/β-catenin, MAPK, PI3K/

AKT, etc. (Wang et al. 2016) that are actively involved in cell cycle progression (Vadlakonda et al. 2013) and deregulation of which has been often reported in NSCLC (Akiri et al. 2009; Ciuffreda et al. 2014). Additionally, therapeutic agent like evodiamine was also used to suppress proliferation and induce apoptosis in human NSCLC cells successfully through blocking MTDH expression (Zou et al. 2015). However, the oncogenic role of MTDH in NSCLC was contradicted in only one investigation (Yao et al. 2014); the discrepancy might be due to racial and ethnic differences in the patient population and/or differences in clinical stages and grades of tumors included in the study from that of other investigations (Zhang et al. 2018; Guo et al. 2020). HEY2 is a transcription factor of bHLH (basic helix–loop–helix) family and a direct target of notch signaling pathway (Fischer et al. 2004). Alteration of notch pathway was noted in NSCLC (Lee et al. 2008) and over-expression of HEY2 was also found in tumor tissue compared to adjacent normal (Westhoff et al. 2009). Therefore, in NSCLC, *PRNCR1* influenced deregulation of miR-126-5p/MTDH and miR-448/HEY2 networks by sponging its target miRNAs and this might contribute significantly to the process of tumorigenesis through associated signaling pathways.

Oral squamous cell carcinoma

In oral squamous cell carcinoma (OSCC) and tongue squamous cell carcinoma (TSCC), the most common type of OSCC, *PRNCR1* over-expression was reported in primary tumors as well as in cancer cell lines (Liu et al. 2021; Lin et al. 2020). Following *PRNCR1* knockdown reduced tumor phenotypes of cancer cells like proliferation, migration, and invasion suggested the association of the lncRNA in disease pathogenesis. Moreover after *PRNCR1* knockdown, TSCC cells also showed increased apoptosis in vitro and reduced growth in tumor xenograft (Lin et al. 2020).

In oral cancer, *PRNCR1* was found to exert its oncogenic impact through sponging target miRNAs (Fig. 3E). miR-326 was reported as a downstream target of *PRNCR1* in OSCC cells leading to the up-regulated expression of Fascin actin-bundling protein-1 (FSCN-1) (Liu et al. 2021); in OSCC, FSCN-1 was over-expressed and found to mediate the activation of positive cell cycle regulators like AKT, ERK and JNK (Alam et al. 2012). miR-326 was found to have lethal effect on OSCC cells (Lindenbergh-van der Plas et al. 2013) and over-expression of FSCN-1 was shown to be associated with poor patient outcome (Chen et al. 2019). Thus, over-expression of miR-326 and subsequent down-regulation of FSCN-1 in oral tumor seemed to be an effective strategy of disease management and this might be achieved through targeting *PRNCR1* by novel therapeutic measures. In TSCC cells, *PRNCR1* was found to attenuate mir-944 and thereby up-regulate expression of HOXB5 (Lin

et al. 2020), a transcription factor over-expressed in head and neck tumors; also in oral cells, HOXB5 was found to involve in the transcriptional up-regulation of EGFR and thereby mediate the activation of AKT/Wnt/β-catenin signaling axis (Lee et al. 2020) associated with the cell cycle regulation (Vadlakonda et al. 2013). Moreover, although tumor-suppressive role of miR-944 was reported in breast and colorectal cancers (Flores-Pérez et al. 2016; Wen et al. 2017), the miRNA was found to be over-expressed and play an oncogenic role in cervical carcinoma (Park et al. 2019) and interestingly in tobacco-induced oral cancer (Peng et al. 2020). Thus, functional role of miR-944 may be oncogenic or tumor-suppressive depending upon upstream modulators (lncRNAs) and downstream target mRNAs and these seem to differ in primary oral tumors under the influence of tumor-specific microenvironment from that of cultured oral cancer cells and hence may contribute to the associated discrepant findings.

Colorectal cancer

PRNCR1 over-expression was reported in primary colorectal carcinoma (CRC) compared to adjacent noncancerous tissue (Yang et al. 2016). *PRNCR1* was also over-expressed in CRC cell lines and after its (*PRNCR1*) knockdown, cell proliferation was inhibited through cell cycle arrest at G0/G1 phase; however, rate of apoptotic cell death remained unaffected and also no significant change was observed in cell migration and invasion properties.

PRNCR1 as potential clinical biomarker in cancer

The *PRNCR1* expression level in tumor was shown to have diagnostic and prognostic importance in different human malignancies (Table 1). *PRNCR1* locus also harbors many SNPs (genetic variants) some of which showed association with the disease prognosis. In addition, significant association of *PRNCR1* SNPs was also reported with the cancer susceptibility in different case–control studies (Table 2).

Prostate cancer

PRNCR1 expression level was not found as a significant predictor for cancer-specific mortality of patients in one investigation (Prensner et al. 2014); but the finding needs further validation as the investigators failed to establish any functional role of the lncRNA in pathogenesis of prostate cancer. Among single-nucleotide polymorphisms (SNPs) of *PRNCR1*, significant association of rs16901979 was found with tumor Gleason Scores in French West Indies population (Cancel-Tassin et al. 2015). In prostate cancer, Gleason Score is evaluated histopathologically to assess the disease prognosis (Egevad et al. 2002). Therefore, rs16901979

seems to have prognostic importance in prostate cancer that needs to be validated in different patient populations with an aim to develop comparatively less-invasive disease biomarker.

In a case–control study with Iranian population, significant association of *PRNCR1* SNPs, rs13252298 (A/G), rs1456315 (A/G), and rs7841060 (T/G) was found with prostate cancer susceptibility, and 'G' was found as the risk allele (Sattarifard et al. 2017); moreover, the SNPs remained in linkage disequilibrium (LD) with another *PRNCR1* variant (rs7007694, T/C), and the haplotypes GTGG (rs1456315G/rs7007694T/rs7841060G/rs13252298G) and GTGA were found to be associated with higher disease risk compared to ATTG in the studied population. In other studies, significant association of rs1016343 (C/T) in Chinese populations (Zheng et al. 2010; Hui et al. 2014) and rs13254738 (C/A), rs16901979 (C/A), rs1016343, and rs1456315 in Japanese populations (Yamada et al. 2009; Takata et al. 2010) was reported with the risk of developing prostate cancer. Moreover, in a study conducted on patients of John Hopkins hospital, significant association of rs16901979 was found with the risk of hereditary prostate cancer, but not with risk of non-hereditary disease subtype (Sun et al. 2008). However, on the contrary, no link of the SNP (rs16901979) was established with disease risk in two independent studies on Ashkenazi Jewish and Jamaican populations (Vijai et al. 2011; Cropp et al. 2014).

Breast cancer

PRNCR1 expression level was suggested as a potential diagnostic biomarker in breast cancer (Abdollahzadeh et al. 2020). In ROC (receiver operating characteristic) curve analysis, the optimal cut-off score for *PRNCR1* expression was determined with respect to maximum sensitivity and specificity in distinguishing breast tumor from adjacent non-tumor and also from clinically healthy normal tissue. Moreover in breast cancer, significant association of *PRNCR1* expression level with increasing tumor size, advanced clinical stages, lymph node metastasis and poor patient survival suggested its importance as a potential prognostic biomarker (Abdollahzadeh et al. 2020; Guo et al. 2019; Ouyang et al. 2021). Interestingly, in breast tumors negative for estrogen receptor (ER) and Her2, significantly higher expression level of *PRNCR1* was detected compared to tumors positive for the markers (Abdollahzadeh et al. 2020). Categorization of breast tumors based on ER, PR (progesterone receptor) and Her2 expression status (positive/negative) is a common practice to determine therapeutic modalities (Onitilo et al. 2009). Tumors negative for ER, PR and Her2 (Triple negative breast cancer) show poor response to the conventional therapies using tamoxifen or herceptin and therefore usually have worse

Table 2 Summary of major *PRNCR1* SNPs associated with cancer susceptibility in different populations

SNP	Risk genotype	Cancer susceptibility	Studied population	References
rs13252298 (A/G)	GG	Prostate cancer (↑)	Iranian	Sattarifard et al. (2017)
	AG	Colorectal cancer (↓)	Chinese	Li et al. (2013)
	AG	Gastric cancer (↑)	Chinese	Li et al. (2016a)
	GG	i. Intestinal type gastric cancer (↑) ii. Gastric cancer in subjects ≥ 60 years with lymph node metastasis (↑) iii. Gastric cancer in subjects ≥ 60 years with tumor stage III (↑)	Korean	Hong et al. (2019)
	GG	i. Lung cancer (↑) ii. Non-small cell lung cancer (↑)	Chinese	Li et al. (2021b)
rs1456315 (A/G) or (C/T)	AG	Prostate cancer (↑)	Iranian	Sattarifard et al. (2017)
	GG	Gastric cancer (↓)	Chinese	Li et al. (2016a)
	CC CC + CT	i. Colorectal cancer (↑) ii. Colorectal cancer in younger (≤ 57 years) individuals (↑) iii. Colorectal cancer in female (↑) iv. Cancer at colon (not at rectum) (↑)	Saudi	AlMutairi et al. (2019)
	GG	i. Lung cancer (↑) ii. Non-small cell lung cancer (↑)	Chinese	Li et al. (2021b)
rs7841060 (T/G)	TG	Prostate cancer (↑)	Iranian	Sattarifard et al. (2017)
rs16901979 (C/A)	CA + AA	Hereditary prostate cancer (↑)	European	Sun et al. (2008)
rs1016343 (C/T)	CT + TT	Prostate cancer (↑)	Chinese	Zheng et al. (2010)
	TT	Prostate cancer (↑)	Chinese (North) population	Hui et al. (2014)
	TT	Gastric cancer in subjects < 60 years with no lymph node metastasis (↓)	Korean	Hong et al. (2019)
rs16901946 (A/G)	GG AG + GG	i. Gastric cancer (↑) ii. Gastric cancer in subjects ≤ 60 years(↑) iii. Gastric cancer in male (↑) iv. Gastric cancer in subjects with *Helicobater pylori* infection (↑)	Chinese	He et al. (2017)
rs7007694	CT and CC	Gastric cancer (↓)	Chinese	Li et al. (2016a)

SNP single-nucleotide polymorphism

↑: increased susceptibility; ↓: decreased susceptibility

prognosis (Al-Mahmood et al. 2018). Higher *PRNCR1* level in ER and Her2-negative breast tumors raised the candidature of the lncRNA as target for novel therapeutic with an aim for better management of the disease subtype.

Oral squamous cell carcinoma

In one investigation, malignant tongue tumors were categorized as of high and low *PRNCR1* levels taking the median value of the expression as a cut-off; significant association of high *PRNCR1* level in tumor was found with parameters of disease progression like increased tumor size, higher clinical stage, and incidence of lymph node metastasis (Lin et al. 2020). Furthermore, significantly shorter overall survival of the patients having high *PRNCR1* level in tumors than those with low expression level indicated potential of the lncRNA in predicting disease prognosis.

Colorectal cancer

In colorectal carcinoma (CRC), *PRNCR1* level showed higher AUC (area under curve) value in ROC curve analysis than conventional serum based biomarker (CEA-CA199) and hence was proposed as more sensitive one for diagnosing the disease condition (Yang et al. 2016). Higher *PRNCR1* expression level was significantly more frequent in tumors of large volume and this indicated possible association of the lncRNA in disease progression; however, the investigators failed to establish any association of *PRNCR1* with other clinico-pathological features like tumor TNM stage and differentiation. Among *PRNCR1* SNPs, risk allele (G) of rs1456315 was found to be associated with increased tumor size and poor differentiation of CRC in Chinese population (Li et al. 2013). Tumor differentiation (histologic grade) was reported as stage independent prognostic factor for patients having CRC (Alexander et al. 2005). Therefore, rs1456315

seems to have prognostic importance in CRC that needs to be validated in other patient populations and moreover functional analysis of the SNP should also be done to explore the underlying molecular mechanism.

Individual susceptibility for developing CRC was found to be influenced by *PRNCR1* variants. In a Chinese population, significant association of AG genotype and G allele of rs13252298 was noted with decreased CRC risk compared to AA genotype and A allele, respectively (Li et al. 2013). In a Saudi population, rs1456315 (T/C) was linked with CRC susceptibility; minor allele 'C' was found as the risk allele and CC genotype, as well as CC + CT additive genotypes, showed significant association with increased disease risk (AlMutairi et al. 2019). The authors also noticed significant association of the SNP (rs1456315) with disease susceptibility in younger individuals (≤ 57 years) and females; moreover, the SNP was found to be associated in predisposing individuals for developing tumors particularly at the colon but not at the rectum. As a functional consequence of 'T' > 'C' allelic substitution of rs1456315, alteration in the secondary structure of *PRNCR1* was suggested with a change in minimum free energy level ($- 85.70$ kcal/mol to $- 85.10$ kcal/mol) and base pairing probabilities (AlMutairi et al. 2019); but the finding was not validated in wet lab experiments and associated molecular pathway remained unexplored.

Gastric cancer

Prognostic importance of *PRNCR1* SNP rs12682421 (G/A) was explored in gastric cancer (GC) in a Chinese population (Zhang et al. 2020); patients carrying AA genotype for the SNP was found to experience higher death incidence than those with GG and GA. However, the finding needs to be replicated before its implementation to predict patient outcome so that personalized therapeutic strategies may be designed in accordance. In bioinformatics analysis, 'A' allele of rs12682421 was shown to facilitate binding of *PRNCR1* with glucocorticoid receptor β (GR-β) and the phenomenon was hypothesized to contribute poor prognosis of GC patients (Zhang et al. 2020). GR-β is a transcription factor that lacks glucocorticoid binding site and acts as inhibitor for transcriptional activity of its alternatively spliced isoform GR-α (Yudt et al. 2003). GR-β is pro-inflammatory in function and has been found to promote aggressive tumor phenotype (cell migration) in bladder cancer and glioma (McBeth et al. 2016; Yin et al. 2013). But the role of GR-β in the pathogenesis of GC is not well characterized and a very low/undetectable expression level of the receptor has been found in gastric tumors (Block et al. 2017). Furthermore, in existing literature, although glucocorticoid receptor was found to interact with lncRNA, such interaction was mediated competitively through DNA-binding domain of the receptor leading to inactivation of its transcriptional activity (Parsonnet

et al. 2019). Therefore, in the study done by Zhang et al., bioinformatics finding for interaction of *PRNCR1* with GR-β needs to be validated in wet lab experiments and potential impact of such interaction on GR-β should be assessed in functional analysis.

PRNCR1 SNPs were also studied in connection with GC susceptibility. In a Chinese population, AG genotype of rs13252298 showed significant association with increased risk of gastric cancer (GC), while CT and CC genotypes of rs7007694 (C/G/T) and GG genotype of rs1456315 (A/G/T) were associated with significantly decreased disease risk (Li et al. 2016a). In one more study with the Chinese population, G allele of *PRNCR1* SNP rs16901946 (A/G) was shown to be associated with GC risk (He et al. 2017); moreover, among the carriers of risk allele, significantly increased GC susceptibility in male, individuals aged ≤ 60 years and in those having *Helicobacter pylori* infection suggested potential interaction of the SNP genotypes with gender, age, and bacterial infection toward predisposition to the disease. In Korean population, TT genotype of rs1016343 was found to be associated with significantly decreased risk of GC negative for lymph node metastasis (LNM) in < 60-year-old subjects (Hong et al. 2019). The study also found significant association of GG genotype of rs13252298 with higher risk of intestinal-type GC which is more frequently linked to dietary and environmental factors than diffuse-type GC in which genetic contribution is mostly highlighted (Hu et al. 2012). In addition, when GC subtypes were considered together and age-stratified, the study found significant association of the SNP genotype (GG, rs13252298) with higher GC risk of tumor stage III and positive LNM in subjects of ≥ 60 years (Hong et al. 2019).

Lung cancer

Among *PRNCR1* SNPs, rs13252298 and rs1456315 were found to influence the susceptibility of lung cancer (LC) and non-small cell lung cancer (NSCLC) in a Chinese northeast population (Li et al. 2021b). Surprisingly the authors did not find significant interaction of the SNPs with cigarette smoking and the variants were found to be associated with the disease susceptibility (LC & NSCLC) of females only but not in males. NSCLC incidence was also reported among never smokers especially females and the disease subset was considered to have a unique genetic predisposition (Devesa et al. 2005; Santoro et al. 2011) to which *PRNCR1* SNPs seemed to have a significant contribution.

Considering diagnostic and prognostic importance of *PRNCR1* expression level in tumor, sensitivity and specificity scores should be evaluated more extensively before introducing the criteria in routine clinical practice for associated malignant conditions. The associations of *PRNCR1* SNPs with cancer susceptibility in different populations need

to be replicated so that the information can be explored as components of disease risk prediction models that may be useful to identify individuals at elevated risk (Wen et al. 2016; Hosono et al. 2016). However, some *PRNCR1* variants also showed association for decreased susceptibility to certain malignancies and this might be due to genetic variability specific to the ethnicity of the studied population and differential interaction of SNP genotypes with disease-specific risk factors. Similarly, genetic variants of other oncogenic lncRNAs like *PCAT1* and *MALAT1* were also found to be associated with decreased susceptibilities to bladder and lung cancers, respectively (Lin et al. 2017; Chen et al. 2021a). *PRNCR1* SNPs are located in exon-1 and are non-coding as the gene encodes for an lncRNA. But, allelic variations at SNP site seemed to affect the secondary structure of *PRNCR1* (AlMutairi et al. 2019). In lncRNAs like *MALAT1*, *HOTAIR*, *SRA* and *MEG3*, secondary structure was reported to play vital functional role (Brown et al. 2012; Somarowthu et al. 2015; Novikova et al. 2012; Zhang et al. 2010). Moreover, in lncRNA, allelic variations of exonic SNP might contribute to loss/gain of miRNA target site (Miao et al. 2018) and the role of *PRNCR1* as a miRNA sponge is well established (Cheng et al. 2018; Ouyang et al. 2021; Guo et al. 2020). Therefore, in *PRNCR1*, impact of the SNPs in connection to all possible functional aspects of the lncRNA need to be analyzed in details to explore the molecular basis for association of the variants with cancer susceptibility.

Therapeutic importance of *PRNCR1*

Frequent over-expression of *PRNCR1* in malignancies and its association with adverse tumor phenotypes and poor patient outcome suggested importance of the lncRNA as a potential target for novel cancer therapeutics (Guo et al. 2019; Abdollahzadeh et al. 2020; Lin et al. 2020; Yang et al. 2016). Oncogenic lncRNAs are commonly targeted at post-transcriptional level by RNA interference (RNAi), antisense oligonucleotides (ASOs) and morpholino ASOs (block RNA function sterically) for therapeutic purpose; however, CRISPR/Cas9-mediated transcriptional silencing of gene locus is also considered as an important strategy (Arun et al. 2018).

In cell line-based experiments, *PRNCR1* was knocked down post-transcriptionally by siRNA in breast cancer (Pang et al. 2019) and by ASO in colorectal cancer (Yang et al. 2016). In oral cancer, siRNA-mediated knock-down of *PRNCR1* was successfully accomplished in vitro as well as in vivo system, but restricted to the xenograft tumor model only (Lin et al. 2020). However, xenograft tumors, as developed from cultured human cancer cell line, may not have representative histological architecture and cellular complexity of native primary tumors (Becher and Holland

2006). Thus, as a prerequisite of clinical trials, therapeutic strategies targeting *PRNCR1* need to be tested in extensive pre-clinical studies involving chemical carcinogen-induced or genetically engineered animal models. But, the P*RNCR1* locus is found in human only and absence of the gene ortholog in other mammalian species may be a limiting factor for its animal model experimentation. For other oncogenic lncRNAs like *DANCR*, *LINC01296*, *MALAT1*, etc., detailed preclinical research on siRNA/ASO-based techniques was also done in addition to in vitro studies, indicating prospects of the strategy for clinical trials (Chen et al. 2021b).

The interaction of *PRNCR1* with its target miRNAs and proteins (AR, DOT1L, etc.) can be blocked sterically by morpholino ASOs (chemically modified and unable to induce RNAse H activity) designed against specific secondary/tertiary structures of the lncRNA involved at interaction interfaces. Morpholino ASOs can be used to block disease-specific function of an lncRNA (i.e., interaction with one miRNA) leaving other functions unaffected (Lennox and Behlke 2016; Arun et al. 2018); hence, the strategy seems to be superior over others that target the entire lncRNA for transcriptional silencing or degradation. Morpholino ASOs were used successfully to block lncRNAs like *Cyrano*, *NATs* (*natural antisense transcripts*) etc. (Lennox and Behlke 2016); for implementation of the strategy against *PRNCR1*, detailed information on secondary/tertiary structure of the lncRNA determined using advanced tools like SHAPE (Selective 2′ Hydroxyl Acylation analyzed by Primer Extension) and PARIS (Psoralen Analysis of RNA Interactions and Structures), is needed as an essential prerequisite.

Transcriptional silencing of lncRNA can be achieved by CRISPR/Cas9 method. In one study, CRISPR interference (CRISPRi) libraries have been developed to inactivate promoters of 16,401 lncRNA genes loci across the human genome (Liu et al. 2017). Investigators validated the efficiency of the method in suppression of major oncogenic lncRNA loci like *MINCR*, *PVT1*, *DANCR*, *LINC00467*, etc. in human cancer cell lines and also assessed the impact on cellular phenotypes. However, *PRNCR1* promoter is not well characterized and this may restrict the successful designing of single guide RNA (sgRNA) for CRISPR/Cas9-mediated knockdown of the lncRNA locus.

Conclusion and future perspectives

As oncogenic lncRNA, although over-expression of *PRNCR1* has been found in malignancies of different organs, the underlying molecular mechanism remains largely unexplored. Impact of *PRNCR1* on aggressive tumor phenotypes like cell proliferation, migration and invasion should be studied in more details to identify

and characterize associated signaling pathways. Ligand-independent activation of androgen receptor (AR) was frequently reported in castration resistant prostate cancer (CRPC) (Hu et al. 2009; Li et al. 2016b) and the conflicting result was available on role of *PRNCR1* in this connection (Yang et al. 2013; Prensner et al. 2014). CRPC is an aggressive disease subtype with worse prognosis and attempts for improvement of disease outcome by novel therapeutics targeting the AR have been reported (Chiin and Attard 2013; Narayanan 2020). Apart from prostate cancer, aberrant AR activation was also reported in gastric carcinoma, hepatocellular carcinoma, and some subtype of breast cancer (Zhang et al. 2014; Jiang et al. 2014; Ni et al. 2011). Therefore, extensive research is warranted to explore the role of *PRNCR1* in AR signaling pathway with an aim to design novel strategies for the associated malignant conditions. Detail investigation is also warranted regarding discrepant findings on target miRNA and downstream oncogenic effectors of *PRNCR1* in OSCC, breast cancer and NSCLC, respectively. Moreover, the functional role of *PRNCR1* in pathogenesis of CRC is needed to explore in more details for identification and characterization of associated molecular pathways. Recently, lncRNAs are emerging as novel tumor biomarkers due to their stability in exosomes of body fluids like plasma, urine and saliva (Li et al. 2015; Berrondo et al. 2016; Tang et al. 2013). Tumor cells have a tendency to release more exosomes and hence peripheral blood of cancer patients usually contains higher amount of exosomes than that of disease-free control (Melo et al. 2015). *PRNCR1* level in tumor was shown to have diagnostic and prognostic importance and comparatively higher expression level of the lncRNA was also found in blood exosomes of patients of pancreatic carcinoma, hepatocellular carcinoma and colorectal cancer than that of normal control (GSE100063, GSE100206) (Fig. 2D); for clinical implication of the findings, further research is needed to analyze the lncRNA level more extensively in blood as well as other body fluids of diseased and normal individuals in connection with different disease parameters.

Therefore, as per available literature, *PRNCR1* plays vital roles in the pathogenesis of human malignancies molecular basis of which is not fully understood; this seems to open new scope of further research for exploring all possible potentials of the lncRNA in diagnostic, prognostic and therapeutic aspects of associated disease conditions.

Availability of data and material Not applicable.

Code availability Not applicable.

Declarations

Conflict of interest The authors state that they have no competing or financial interest.

Ethical approval Not applicable.

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