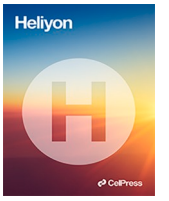
Heliyon 10 (2024) e34950

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

A systematic review of mechanisms of PTEN gene down-regulation mediated by miRNA in prostate cancer

Fernando Bergez-Hernández [1], Martín Irigoyen-Arredondo [1], Alejandra Martínez-Camberos [*]

Laboratorio de Biomedicina y Biología Molecular. Lic. en Ciencias Biomédicas, Universidad Autónoma de Occidente. Av del Mar 1200, Tellerías, 82100, Mazatlán, Sinaloa, Mexico

ARTICLE INFO

Keywords:
miRNA
PTEN
Prostate cancer
Epigenetic regulation

ABSTRACT

Background: The Phosphatase and Tensin Homolog gene (PTEN) is pivotal in regulating diverse cellular processes, including growth, differentiation, proliferation, and cell survival, mainly by modulating the PI3K/AKT/mTOR pathway. Alterations in the expression of the PTEN gene have been associated with epigenetic mechanisms, particularly the regulation by small non-coding RNAs, such as miRNAs. Modifications in the expression levels of miRNAs that control PTEN have been shown to lead to its underexpression. This underexpression, in turn, impacts the PI3K/AKT/mTOR pathway, thereby influencing crucial mechanisms like proliferation and apoptosis, playing an important role in the initiation and progression of prostate cancer (PCa). Thus, we aimed to systematically reviewed available information concerning the regulation of PTEN mediated by miRNA in PCa.

Methods: Electronic databases were searched to identify studies assessing PTEN regulation via PCa miRNAs, the search included combination of the words microRNAs, PTEN and prostatic neoplasms. The quality assessment of the articles included was carried out using an adapted version of SYRCLE and CASP tool.

Results: We included 39 articles that measured the relative gene expression of miRNAs in PCa and their relationship with PTEN regulation. A total of 42 miRNAs were reported involved in the development and progression of PCa via PTEN dysregulation (34 miRNAs up-regulated and eight miRNAs down-regulated). Sixteen miRNAs were shown as the principal regulators for genetic interactions leading to carcinogenesis, being the miR-21 the most reported in PCa associated with PTEN down-regulation. We showed the silencing of PTEN could be promoted by a loop between miR-200b and DNMT1 or by direct targeting of PTEN by microRNAs, leading to the constitutive activation of PI3K/AKT/mTOR and interactions with intermediary genes support apoptosis inhibition, proliferation, invasion, and metastasis in PCa.

Conclusion: According to our review, dysregulation of PTEN mediated mainly by miR-21, -20a, −20b, −93, −106a, and −106b up-regulation has a central role in PCa development and could be potential biomarkers for diagnosis, prognostic, and therapeutic targets.

* Corresponding author.
E-mail addresses: fernando.bergez@uadeo.mx (F. Bergez-Hernández), martin.irigoyen@uadeo.mx (M. Irigoyen-Arredondo), alejandra.martinez@uadeo.mx (A. Martínez-Camberos).

[1] Fernando Bergez-Hernández and Martín Irigoyen-Arredondo contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e34950
Received 15 July 2024; Accepted 18 July 2024
Available online 20 July 2024

1. Introduction

The Phosphatase and Tensin Homolog gene (PTEN) is a pivotal regulator of essential cellular processes encompassing growth, differentiation, proliferation, and survival. Serving as a phosphatase, PTEN exerts a central role in modulating the PI3K/AKT/mTOR signaling pathway, which holds a position in governing cell proliferation and viability [1,2]. PTEN functions by dephosphorylating phosphatidylinositol 3,4,5-trisphosphate (PIP3) to phosphatidylinositol 4,5-bisphosphate (PIP2). This reaction is critical in the PI3K/AKT signaling pathway, where PIP3 acts as a second messenger promoting cell growth, survival, and proliferation. By converting PIP3 back to PIP2, PTEN reduces PIP3 levels, thereby inhibiting the PI3K/AKT pathway and acting as a tumor suppressor. This prevents uncontrolled cell growth and survival, reducing the risk of tumor development [3–5]. The identification of PTEN as a tumor suppressor gene underscores its importance, as disruptions and deficiencies in PTEN are intrinsically linked to the pathogenesis of diverse malignancies, prominently including prostate cancer (PCa) [6,7]. The loss of PTEN, common in various types of cancer due to genetic mutations or deletions, dysregulates the PI3K/AKT pathway, promoting cellular growth and tumor survival [8].

The expression of the PTEN gene is governed by a complex network involving transcription factors, epigenetic modifications, and post-transcriptional mechanisms. Specifically, the emergence of microRNAs (miRNAs), a class of small non-coding RNA molecules, has illuminated a prominent layer of PTEN regulation [9]. These miRNAs interact with the 3′ untranslated region (UTR) of PTEN mRNA, causing either translational inhibition or facilitating degradation. This intricate interaction leads to decreased PTEN protein levels, consequently triggering the activation of the PI3K/AKT/mTOR signaling pathway [10,11].

Evidently, miRNA dysregulation has been implicated in the pathogenesis of various cancer types, including PCa [12]. Numerous miRNAs have been identified as regulators of PTEN within the context of PCa, including miR-21, miR-221/222, and some miRNAs of the miR-17 family [11,13–15]. The regulation of PTEN mRNA transcription and translation is provided by the action of several miRNAs, that contribute to the simultaneous loss of PTEN expression in specific cancers [16]. Dysregulation of these miRNAs directly results in reduced PTEN expression levels, fueling the activation of the PI3K/AKT/mTOR pathway [17]. This molecular cascade ultimately promotes the proliferation and persistence of cancer cells, solidifying the role of miRNAs as pivotal facilitators of tumorigenesis [18].

The comprehensive understanding of PTEN regulation by miRNAs holds profound implications for identifying and developing innovative therapeutic targets in PCa treatment [13,14]. By deciphering the intricacies of this regulatory axis, novel strategies for intervening in cancer progression may emerge. Furthermore, the interplay between PTEN and miRNAs has the potential to shed light on the foundations of various diseases linked to PTEN dysfunction, including autoimmune disorders and inflammatory conditions. This holistic perspective paves the way for a comprehension of PTEN's role, from cellular homeostasis to the intricacies of disease etiology [19].

The interplay between the fundamental PTEN regulator of cellular dynamics and miRNAs, intricate modulators of gene expression, reveals a captivating narrative bridging fundamental cellular processes and the pathogenesis of PCa [20]. The complex web of PTEN regulation via miRNAs underscores their potent role in steering cellular fate and disease trajectory [21] As research advances in this area, new therapeutic interventions and holistic disease understanding are poised to unfold, ultimately reshaping strategies to combat PCa and a spectrum of associated disorders [13,14,19].

Considering the profound implications highlighted in this discussion, the significance of the present study becomes evident. Through a systematic analysis of available information concerning the regulation of PTEN mediated by miRNA in PCa, this study seeks to contribute to the broader understanding of disease etiology and potentially pave the way for novel therapeutic strategies. The ongoing exploration of PTEN regulation remains fundamental in shaping our comprehension of its multifaceted role in health and disease.

2. Materials and methods

The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines [22].

2.1. Literature search

A methodological review of the literature was conducted in March 2023 across the main search engines PubMed (Medline), PubMed Central, and Scopus databases.

The search keywords included both free words and MeSH terms, ensuring all publications with the keywords and related terms in their title or abstract were included: ("microRNAs"[MeSH Terms] OR "microRNAs" [Title/Abstract] OR "miRs" [Title/Abstract] OR "microRNA"[Title/Abstract] OR "miRNA" [Title/Abstract] OR "miR" [Title/Abstract]) AND PTEN[Title/Abstract] AND ("prostatic neoplasms"[MeSH Terms] OR ("prostatic"[Title/Abstract] AND "neoplasms"[Title/Abstract]) OR "prostatic neoplasms"[Title/Abstract] OR ("prostate"[Title/Abstract] AND "cancer"[Title/Abstract]) OR "prostate cancer"[Title/Abstract]). All the records found through the search in the different databases were compiled and downloaded into Zotero 6.0.26 to manage the bibliographic records by the reviewers.

2.2. Study eligibility criteria

A single reviewer removed duplicate records both automatically and manually from the Zotero library. Next, each reviewer

evaluated the studies based on title and abstract screening to remove any non-relevant record, according to their agreement level. After this step, the studies were retrieved in full text to assess final eligibility using a standardized format based on the inclusion criteria. The present review included original articles that measured the relative gene expression of miRNAs in human specimens (tissue or circulation), cell lines, or animal model and their relationship with PTEN regulation in PCa. The exclusion criteria were 1) non-English or Spanish language studies, 2) the study was a meta-analysis, review, comment, letter, conference abstract, or duplicate publication, 3) studies with incomplete data or full-text unavailability, and 4) insufficient data to match our interests.

The following data were extracted from each eligible study and organized in tables: the surname of the first author, publication

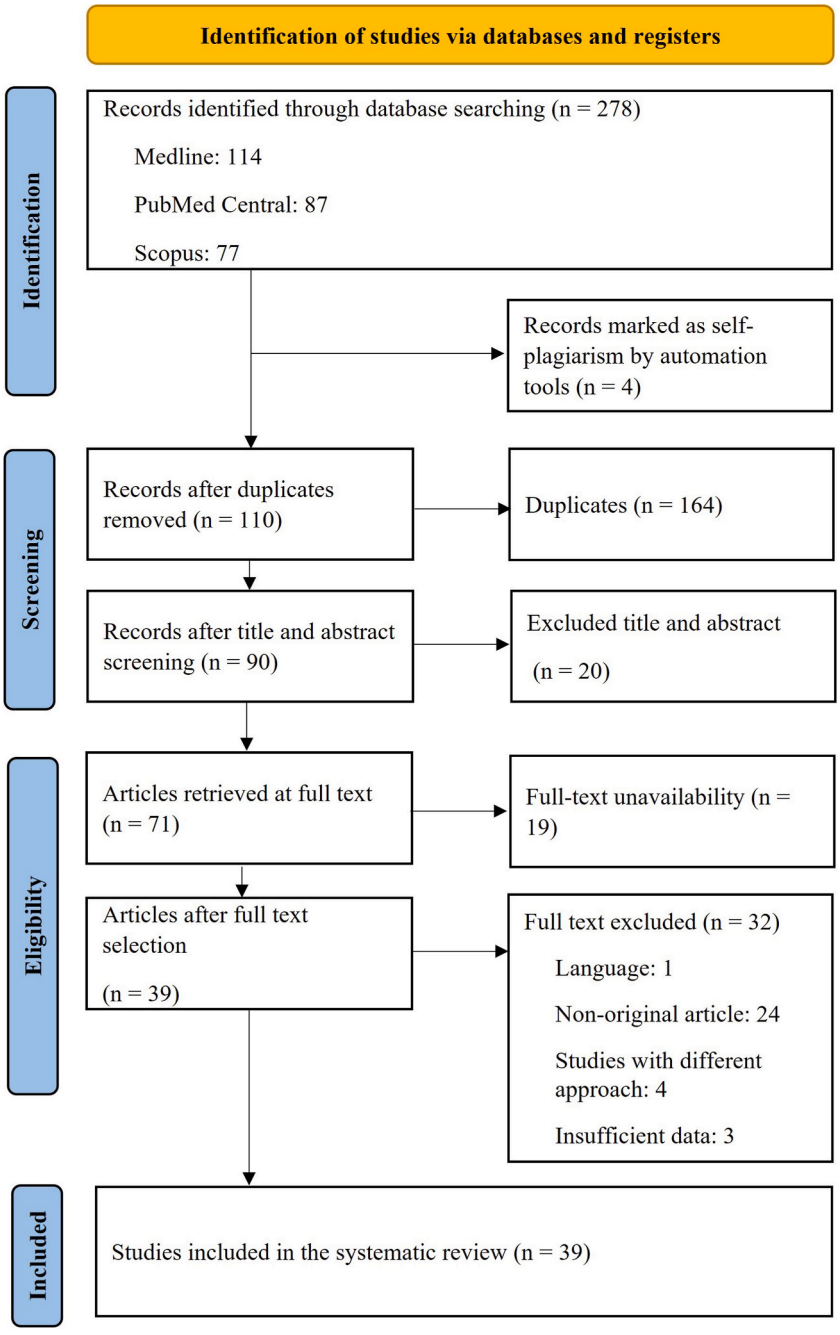


Fig. 1. PRISMA flow diagram of the articles selection process. Flowchart illustrating the search strategy used to identify association studies of miRNAs expression involved in PTEN for inclusion in the systematic review.
Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372:n71. https://doi.org/10.1136/bmj.n71

Table 1
Characteristics of the studies included in the systematic review.

Author, Year	Type of sample			Population/ Country	No. of patients	miRNAs expression
	Cancer cell line	Animal model	Human specimen			
Ngalame, N. 2014	RWPE-1, CAsE-PE, As-CSC			USA		*miR-let-7, miR-7, miR-9, miR-10b, miR-34a, miR-34c-5p, miR-96, miR-98, miR-125a-5p, miR-125b, miR-126, miR-127–5p, miR-134, miR-135b, miR-138, miR-143, miR-146b-5p, miR-148a, miR-373, miR-155, miR138, miR181a, miR-181b, miR-181c, miR-181d, miR-181c, miR-183, miR-193b, miR-196a, miR-205, miR-218, miR-222, miR-355, let-7b, let-7i, let-7e, let29b
Khan, M. 2022	*Database*			India		*miR-let-7b, miR-21, miR-155–5p, miR-181b-1, miR-548
Dhar, S, 2011	DU145, LNCaP			USA		*miR-17, miR-92, miR-106b
Dhar, S. 2015	DU145, 22Rv1	Fox n1 $^{nu/nu}$ male mice (7 weeks)	–	USA		↑miR-17, miR-20a, miR106a, miR-106b
Poliseno, L. 2010	DU145, Ca-HpV-10, LNCaP, MDA-PCa-2b, PC3, U2OS, 22Rv1	NCR nude mice (4–6 weeks)	Prostatic tissue	USA	184	↑miR-19a, miR-22, miR-25, miR-93, miR- 106b
Tian, 2013	DU145, LNCaP, 22RV1	–	–	China		↑miR-19b, miR-23b, miR-26a, miR-92a
Farina, N. 2016	TRAMP-C2 cells	TRAMP mice		USA		*miR-20a-5p, miR-20b-5p, miR-23b-5p, miR-27a-3p, miR-27b-3p, miR-30a-5p, miR-30c-5p, miR-30e-5p, miR-93–5p, miR-135a-5p, miR-135b-5p, miR-139–5p, miR-141–3p, miR-181a-5p, miR-200a-3p, miR-200b-3p, miR-203–3p, miR-204–5p, miR-205–5p, miR-214–3p, miR-218–5p, miR-221–3p, miR-320-3′, miR-324–5p, miR-340–5p, miR-375–3p, miR-382–5p, miR-384–5p
Wang, G, 2013	DU145	Mice	Prostatic tissue	USA	42	↑miR-20a, 93, 106b
Guo, J, 2017	PC3, VCaP	–	Prostatic tissue	China	35	↑miR-20b
Zhou, B, 2016	DU145	Balb/c athymic nude mice (6-8-weeks)	–	China		↑miR-21
Yang, C. 2010	DU145, PC3	–	–	USA		↑miR-21
Liu, LZ, 2011	DU145	–	–	–		↑miR-21
Zhao, W, 2021	PC3, DOX- resistant PC3/DOX	–	–	China		↑miR-21
Yang, Y, 2016	PC3	–	–	China		miR-21
Kim, K, 2020	DU145, PC3	Balb/c nude mice (12–16 weeks)	–	South Korea		miR-21
Zhu, L, 2018	LNCaP, PC3	–	Blood	China	158	↑miR-21
Folini, M, 2010	DU145 and PC-3		Prostatic tissue	Italy	36	*miR-21
Kshirsagar, P. 2022	–	Mice	Serum	USA	85	↑miR-21, miR-141, miR-375
Budd, W. 2015	M2182, M12, p69	–	Prostatic tissue	USA	5	↑miR-22–3p
Li, J. 2016	DU145, PC3	–	–	–	.	↑miR-23c, miR-32–5p, miR-488–3p, miR-3673, miR-3654 ↓miR-3176 miR-141–3p
Belair, C. 2015	–	Mice MMRRC:32051	–	USA		↓miR-31, 93, 139, 183, 210
Latonen, L. 2017		FVB/N mice		Finland		*miR-32
Gurbuz, V, 2021	–	–	Blood	Turkey	90	↑miR-34c, miR-148a, miR-152 ↓miR-200b
Yanshen Z, 2021	LNCap, PC3	–	–	China		↑miR-92a
Lu, J, 2019	PC3	–	Prostatic tissue	China	32	↑miR-106a
Gao, S, 2018	DU145, LNCaP, PC3	–	Prostatic tissue	China	50	↑miR-146b

(*continued on next page*)

Table 1 (*continued*)

Author, Year	Type of sample			Population/ Country	No. of patients	miRNAs expression
	Cancer cell line	Animal model	Human specimen			
Aboushousha, T. 2021	–	–	Prostatic tissue	Egypt	100	↑miR-153
Wu,Z, 2012	DU145, 22Rv1	–	–	China		↑miR-153
Ding, X, 2021	DU145, C4–2B, LAPC4, LNCaP	–	–	China		↑miR-181a-5p
Takao, A. 2018	PTEN-knockout cell line: ΔPTEN	–	–	Japan		↑miR-210–3p
Fang Y, 2019	PC3	–	Serum	China	241	↑miR-214
Zhang, Y, 2018	DU145, PC3	–	Prostatic tissue	China	164	↑miR-410–3p
Albino, D, 2021	LNCaP, RWPE-1	NSG male mice (4–6 weeks)	Plasma	Portugal, South Africa, Switzerland	64	↑miR-424
Duan, XM, 2019	DU145, LNCaP	–	–	China		↑miR-498
Tan, G, 2020	DU145, PC3	Male BALB/c nude mouse (36–38 weeks)	Prostatic tissue	China	156	↑miR-503–5p
Saffari, 2019	–		Prostatic tissue	Iran	93	↑miR-548c-3p
Zang, M, 2021	LNCaP, PC3	–	Prostatic tissue	China	43	↑miR-572
Zhang, S. 2020	C4-2, DU145, LNCaP, PC3, 22Rv1,	Female BALB/c nude mouse (5 weeks) (Tumor xenograft assay)	Prostatic tissue	China	49	↑miR-616
Nip, H, 2016	DU145, LAPC4, MDAPCa2b	Athymic nude mice	–	USA	196	↑miR-4534

**miRNAs expression is not significantly associated with PTEN dysregulation*

year, title, geographical region where the study was conducted, miRNA(s) investigated, sample size, sample type, detection method, results of miRNAs and PTEN deregulation and outcome details of the molecular assessments. The reviewers individually evaluated the articles without differences in data collection. Any discrepancies between reviewers about the inclusion or exclusion of studies were discussed to reach a consensus.

As a quality assessment, the risk of bias was evaluated using an adapted version of the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) based on the Cochrane Collaboration RoB Tool [23] and the Critical Appraisal Skills Programme (CASP) [24]. We assess the following domains in our study: 1) selection, defined by a clear description of selection criteria, characteristics of the study population, and group assignment; 2) performance, defined as a clear specification of the method used in the development of the research; 3) detection, defined as the explicit description of how the outcomes were analyzed and presented the association with PTEN expression; 4) attrition defined as the omission of missing data without tracking or explaining the discrepancies or differences; and 5) reporting, defined as the presentation of results without discrepancies and similarity to other reports. Each study was assessed for having a low, high, or unclear bias risk in each defined domain.

3. Results

3.1. Study selection and characteristics

A total of 278 studies were found in the initial literature search. As presented in the selection process (Fig. 1), 164 studies were removed due to duplication. After reviewing abstracts and full texts, 39 literatures were included according to the selection criteria.

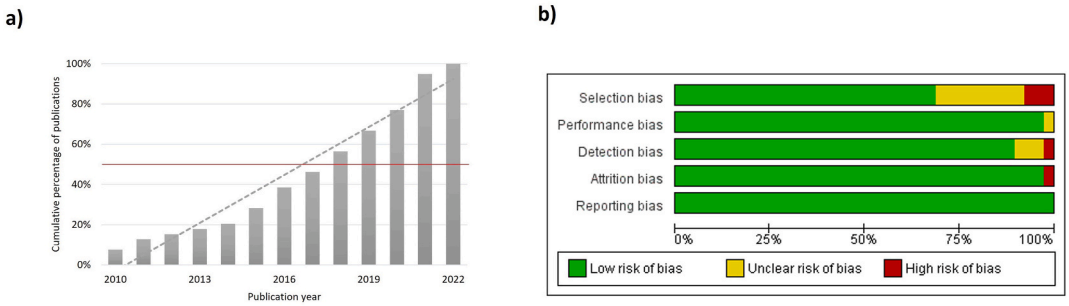


Fig. 2. a) Publications per year, and b) risk of bias assessment.

The characteristics of the included studies are summarized in Table 1. The publication years of these records ranged from 2010 to 2022, according to Fig. 2a, 52.5 % of the studies were published between 2018 and 2022, thus indicating a high interest in the topic in recent years. The publications were from 13 different countries on four continents, with Asia contributing the highest number of publications (59.5 %), China the major country with 50 % of all the publications, followed by the United States with 26.2 % in America.

Accordingly, each study was assessed for having a low, high, or unclear risk of bias in each of the following criteria: 1) selection, 2) performance, 3) detection, 4) attrition, and 5) reporting bias. The results from this evaluation are presented as the percentage of studies in each category of bias per criteria. Fig. 2b summarizes the risk of bias assessment across all included studies. The major area of bias was the selection stage, 7.69 % and 23.08 % of the studies had a high or unclear risk of bias, respectively, primarily for not presenting a clear description of the initial characteristics of the population analyzed.

Most study designs were experimentally developed in prostatic cell lines or animal models, 85 % of studies analyzed miRNAs and PTEN expressions using qPCR; less frequent detection methods were microarrays, miRseq, and *in situ* hybridization. Analysis of PTEN protein was mainly realized by Western blot and luciferase +3′UTR reporter assays for assessment of the interaction between PTEN and miRNAs.

The articles included in this review are presented grouped according to the reported association with the down-regulation of PTEN and promotion of PCa, as well as a review of the main mechanisms involved in the deregulation of miRNAs and the therapeutic potential of these biomarkers. The main findings are described below.

3.2. miR-21

The miR-21 is one of the most reported miRNAs related to the regulation of PTEN expression in PCa. Many reports indicate that this is key in the processes of tumorigenesis and the events after PTEN blockade. In this context, it has been observed that PTEN is overexpressed in cells that do not express miR-21, suggesting that PTEN is a target of miR-21 in DU145 cells. Furthermore, miR-21 reduces PTEN levels through a STAT3-dependent pathway and increases AKT activity, concluding that miR-21 can activate AKT through a PTEN-independent pathway involving overexpression of the p85 PI3K subunit [25]. In a different approach, the expression of miR-21 in PTEN knock-out and wild-type mice has been evaluated and it is observed that mice that do not express PTEN have high levels of miR-21 [26]. In addition, it has been observed that miR-21 induces the expression of HIF-1a and VEGF when targeting PTEN, regulating the AKT and ERK pathways, and leading to angiogenesis in PCa [27]. It has been verified that miR-21 can bind to the 3′ UTR region of PTEN in LNCaP cells, thus suggesting that PTEN, a regulator of apoptosis, is a target of this miRNA, being involved in the pathogenesis of PCa [28].

Several studies have been carried out blocking the expression of miR-21 to understand its functions, for example, it has been observed that when transfecting a miR-21 analog, the expression of PTEN was decreased and PI3K and AKT were elevated, confirming that miR-21 can target PTEN and inhibit its expression and increase the function of the PI3K/AKT pathways in PCa cells [29]. Likewise, it has been observed that when the expression of miR-21 decreases, the expression of PTEN and the Pdcd4 protein rise [30]. It is suggested that suppressing the expression of miR-21 could be interesting as a possible therapy for metastatic PCa since administering anti-miR21 induced the de-repression of the PTEN protein. In their analyses, they used a bone metastatic tumor model to investigate the effectiveness of this anti-miR21, which successfully prevented metastasis [31]. Similarly, another research group observed that when administering an inhibitor of miR-21 in cell lines, the expression of PTEN was increased. The authors suggest that miR-21 silencing may be involved in reversing multidrug resistance of PCa cells, through some molecular mechanisms, such as increased PTEN activity and repression of the PI3K/AKT pathway [32]. One of the most recent studies performed a bioinformatic analysis, taking information from various databases and establishing different molecular signaling pathways in PCa. Their results show that miR-21 is significantly associated with PTEN, the authors observed that miR-21 can repress PTEN expression. Likewise, they report that this key gene significantly correlates with average PCa survival [33].

In this review, only one report was identified that contradicts what was previously stated, the authors reported that miR-21 is not essential in PCa and by blocking, it is not enough to counteract the proliferative potential of PCa cells or to modify the sensitivity of these to anticancer drugs or radiation. Similarly, no biological response was observed when suppressing or increasing miRNA, nor were significant differences identified between tumor and normal tissue. No correlation was observed between the expression of miRNA and PTEN, concluding that the 3′ UTR region of PTEN could be inaccessible to miRNA due to folding or mutations that prevent interaction with miR-21, making it impossible for it to be regulated by this miRNA [34].

3.3. mir17 family

The miR-17 family, a subgroup of miRNAs, stands out as a crucial regulatory player in cellular processes. This family exhibits intricate connections with diverse physiological and pathological phenomena. With their ability to modulate gene expression by binding to specific target mRNAs, the miR-17 family miRNAs emerge as vital components in various biological contexts, including cancer development, cellular proliferation, and differentiation.

Using computational tools, the putative gene targets of oncogenic and tumor suppressor miRNAs using sequence complementarity of the seed region were determined. They identified miR-17 family members including: miR-17, miR-20a, miR-20b, miR-106a, and miR-106b. These were recognized as oncogenic miRNAs [35]. Besides, they established that PTEN gene was a target of miRNAs miR-17, miR-20a, miR-106a, and miR-106b. Additionally, they used cell lines, which included a PTEN-positive cell line, that was subsequently Xenografted into mice [36].

Other studies have characterized the miR-17 family, revealing their role as regulators of the PTEN gene. They pinpointed the

positions of their seed matches within the 3′UTR of the PTEN gene and it was established that, within this specific family, miR-93 and -106b were under-expressed in PCa. To corroborate that miR-93, and -106b indeed target PTEN, PTEN levels were quantified via immunohistochemistry (IHC). Remarkably, a significant and inverse correlation between PTEN and miRNAs [37].

In line with earlier findings, another study unveiled that those members of this family, specifically miR-20a, −93, and −106b, target the PTEN gene. Subsequent analysis of their expression levels in human PCa tissue in comparison to healthy tissue revealed significant overexpression of these miRNAs in cancer. This study's results collectively imply a noteworthy up-regulation of the miRNA family in human PCa [38].

Moreover, bioinformatics analysis predicted PTEN as a potential target gene for miR-20b in PCa. Using dual luciferase reporter assays and Western blot analysis, was demonstrated that restoration of PTEN expression did not impact endogenous miR-20b levels in PCa. This underscores that miR-20b fosters cellular proliferation and migration by directly regulating PTEN in PCa. Critically, the suppression of miR-20b expression exhibits an *in vitro* antitumor effect [39]. Equally compelling to note is the striking observation that in PTEN-negative or null epithelial cells, an array of distinct miRNAs are conspicuously overexpressed, with miR-93 notably taking the forefront [40].

Finally, within the context of the miR-17 family, an intricate interplay was unveiled, highlighting a discernible linkage between miR-106a and PTEN. Elaborating upon this, examination of PTEN mRNA expression in tumor and normal tissues uncovered a substantial diminution of PTEN mRNA levels within tumor tissues compared to their normal counterparts. It was notably discerned that PTEN overexpression notably curtailed the growth of cellular lineages, consonant with the effects observed upon miR-106a inhibition. These compelling findings collectively infer that miR-106a orchestrates the intricate progression of prostate carcinoma by orchestrating the intricate involvement of PTEN [41].

3.4. *miR-25 family*

Some members of the miR-25 family have been reported to be important regulators of PTEN, including miR-25, -32, −92a, and −92b. It has been identified through bioinformatic analysis that PTEN can be targeted by members of the miR-25 family, including miR-25. Analyses in cell lines comparing primary carcinomas, metastatic and normal cell lines, the authors observed an increase in this miRNA in all lines with cancer, associating it with prostate tumorigenesis. In addition, in their analyses performed on a prostate tumor tissue microarray, they identified an inverse correlation between the abundance of PTEN and miR-25. The authors conclude that this overexpressed miRNA in PCa, together with other miRNAs, decreases the expression of PTEN [37].

It has been observed through bioinformatic analysis using the KEGG tool that miR-32 can regulate PTEN, and that this miRNA is generally overexpressed in PCa. The authors also mentioned that this miRNA can regulate the TCF4 gene, which has been observed to be related to chemotherapy efficiency, where silencing of this gene in cell lines makes it more sensitive to chemotherapy. Therefore, the authors conclude that PTEN may be an important gene that is regulated by miRNAs in chemoresistant cancer cells [42].

Unlike what was mentioned, other studies observed no evidence of PTEN under-expression in mice expressing miR-32 compared to controls. They conclude that this reveals the existing differences between miR-32 targets between human and mouse PCa, between tissue and cell lines, and/or between normal and cancerous tissue [43].

It has been reported that miR-92a, in combination with other miRNAs, promotes the proliferation of prostate cells in PCa by regulating PTEN and its subsequent signaling in an *in vitro* model. The authors observed that this miRNA can interact with the 3′ UTR region of PTEN in PCa and normal prostate cell lines, miR-92a being one of those that potentially has a more important role in that regulation. Also, they conclude that this miRNA acts as an oncogene in PCa, which helps to better understand the molecular mechanisms of PCa related to the regulation of PTEN expression [44].

Similarly, it has been observed that transfecting PCa cell lines with a miR-92a inhibitor significantly increased PTEN protein levels. This suggests that this miRNA plays a key role in the regulation of PCa cell proliferation, migration, and invasion through the regulation of the PTEN/AKT pathway, so the inhibition of this miRNA could be of practical value for future treatments of PCa patients [45].

Also, miR-92b, which is part of the miR-17-92 cluster, has been identified as a regulator of PTEN and is directly associated with PCa tumorigenesis, considering it as an oncomiRNA [35].

3.5. *miR-200 family*

The miR-200 family seems to be critical in the regulation of PTEN expression, with miR-200a, miR-200b, and −141 being reported as potential regulators of the expression of this gene in PCa. It has been observed that there is an indirect relationship between PTEN and miRNAs. The authors observed that miR-200a may have Runx1 gene as a target, and Runx1 is associated with changes in the expression of genes such as PTEN in murine models. They suggest a very important interaction between Runx and miRNAs centered on PTEN-PI3K-AKT signaling [46].

Similarly, it has been observed that miR-200b is significantly associated with the PTEN gene in patients with metastatic PCa, indicating that this miRNA can suppress PTEN expression. Conversely, no relationship was observed between the expression of miR-200a and PTEN. The authors point out that these miRNAs behave as oncomiRNAs in the early stages of PCa and as tumor suppressors in the metastatic stage [47].

Using predictive bioinformatics models, it has been observed that miR-141 can regulate PTEN [42,46]. The authors observed that miR-141 was underexpressed in exosomes derived from chemoresistant PCa cells, suggesting that it could be relevant in the chemoresistance of these cells during repeated oxaliplatin treatments [42].

Lastly, it has been observed in a murine model that lacks the expression of the PTEN gene, that miR-141 was overexpressed in

comparison to wild-type mice. In their analyses carried out on samples from patients with PCa, they observed overexpression of this miRNA compared to control patients [26].

3.6. Regulatory mechanisms of the expression of miRNAs

Several mechanisms could be related to the deregulation in the expression of the PTEN regulatory miRNAs, including changes in gene expression in the miRNA biogenesis machinery and other epigenetic changes. In this context, it has been observed through *in situ* hybridization (ISH) in a microarray of prostate tumor tissue that the increased expression of Dicer, which is a key protein in miRNAs biogenesis, was associated with tumor progression, observing a direct correlation between the overexpression of miRNAs-22, -25, −93 and −106b, suggesting that an aberrant or deregulated maturation process contributes to the increase in the abundance of these miRNAs [37].

In the same context, another essential protein in miRNA biogenesis is the DGCR8 protein. There has been a significant correlation between AKT activation through PTEN and increased levels of DGCR8, this last one is an important component in the miRNA biogenesis machinery, suggesting that AKT activity should require an increase in miRNA biogenesis. In addition, the loss of DGCR8 inhibits and even reverses the tumor progression caused by the loss of PTEN which is associated with the overexpression of miR-31, -93, −139, −183, and −210 [40].

Another molecular mechanism that has been associated with the regulation of miRNA expression is DNA methylation. The main mediators of this mechanism, which are DNA methyltransferases (DNMT), have been studied to understand their implication in miRNA expression. It has been observed that in patients with PCa and metastatic PCa, DNMT1 is overexpressed and the DNMT3a, DNMT3b, and PTEN genes are underexpressed, while some miRNAs are overexpressed. The authors suggest that the increased expression of DNMT1 is associated with high levels of miRNAs, and this increase could be caused by a mutant version of the DNMT1 gene. In addition, miR-200b, which is underexpressed in metastatic patients due to hypermethylation in its promoter, has a synergistic interaction with the DNMT3a and DNMT3b genes, but an antagonistic interaction with DNMT1. The authors indicate that the underexpression of miR-200b stimulates the expression of the DNMT1 gene. Likewise, they suggest that there may be an interesting regulation cycle, where the enzymes in charge of methylation modify the expression of miRNAs, and these, in turn, impact the regulation of these enzymes [47].

3.7. PTEN's influence on prostate cancer-modulating genes

Genetic regulation profoundly shapes the course of PCa initiation and progression. In this context, the PTEN gene emerges as a pivotal player in modulating genes that wield influence over the dynamics of this cancer type. Renowned for its potent tumor-suppressive capabilities, PTEN exerts significant control over a spectrum of intricate cellular processes. This succinct exploration delves into the intricate interplay between PTEN, and genes implicated in the orchestration of PCa regulation, offering a fundamental perspective on its impactful role within this disease. The association of PTEN with the PI3K/AKT pathway has always been of great interest in the etiology of PCa due to its strong interaction within the pathway. Several studies have tried to establish the interaction pathways involving PI3K/AKT/PTEN and their axes of action during the development of prostate proliferation [27,29,37,44,46,48,49].

It is a common occurrence to observe PTEN being underexpressed or silenced during the development and progression of PCa. Several genes have been identified to play a role in this underexpression or silencing, and as a result, become associated with this pathway of interaction. These include AKT, RUNX1, RUNX2, miR-19b, −23b, and −21. The overexpression of these genes contributes to the decrease or suppression of PTEN expression levels [27,29,37,44,46]. Similarly, it has been observed that when PTEN transcript and protein levels are decreased or attenuated, other downstream genes associated with the PI3K/AKT/PTEN pathway are increased. For example, increased mRNA of BCL-XL, VEGFA, PI3K/AKT, Bcl-2, survivin, MMP2, MMP9, Tet1, Twist2, Arg1, Figf, Wnt3, Ptgr1 and p110δ and increased protein levels of BCL2, BCL-XL, VEGFA and HIF-1α are observed [27,29,44,49,50]. Also, it is suggested that the downregulation of PTEN expression levels was caused by the co-expression of the MCM7 protein and the miR-106b∼25 cluster [37].

Other studies reviewed during this systematic review suggest additional types of interactions that are not yet well established but are considered relevant. For instance, the interaction involving miR-181a-5p efficacy in countering the impact of MBNL1-AS1 on PTEN and the PI3K/AKT/mTOR pathway [48]. Another notable interaction is the regulation of miR-152 on DNMT1/DNMT3b/PTEN, which indicates a strong association between miR-152 and DNMT1, and a significant association between DNMT1 and PTEN [47]. Further identified interactions include GAS5, which functions as a key modulator of miR-21 and -1284. These reciprocal interactions regulate PDCD4/PTEN and AKT expressions, respectively [29]. Lastly, the modulation of ZBTB7A mRNA translation, which targets PTEN, shows a significant relationship between the loss of ZBTB7A protein and PTEN, suggesting their collaborative oncosuppressive functions [38].

These insights underscore PTEN's role in regulating PCa-related genes, revealing complex mechanisms governing cancer progression and control.

3.8. Clinical applications of miRNAs in prostate cancer

The routine biomarkers and/or the clinical examination for PCa diagnosis and prognosis have several limitations with low accuracy. Thus, the need for a valuable and accurate biomarker is imperative. The miRNAs are now widely recognized as potential cancer therapeutic targets because they can target several signaling pathways involved in tumor development, metastasis, invasion, and

Table 2
Candidate miRNAs for biomarkers of prostate cancer detection, disease progression, and therapy response.

Purpose	miRNAs candidates	Source	Clinical value	Reference
Diagnostic				
PCa vs HC	miR-21, -141 and −275	Serum	Biomarkers with high accuracy, sensitivity, and specificity (ROC AUC 0.945)	(Kshirsagar et al., 2022)
	miR-34c, −148a and −152	Blood	Upregulation in PCa	(Gurbuz et al., 2021)
	miR-548c-3p	Tissue	Upregulation in PCa vs matched adjacent non-cancerous tissues.	(Saffari et al., 2019)
PCa vs BPH	miR-548c-3p	Tissue	Upregulation more than 2-fold change in high grade PCa vs BPH	
	miR-4534	Tissue	Biomarker with high accuracy, sensitivity, and specificity (ROC AUC 0.900, CI 95 %: 0.834–0.946)	(Nip et al., 2016)
	miR-153	Tissue	Upregulation in PCa	(Aboushousha et al., 2021)
Prognostic				
Low vs High risk	miR-153	Tissue	Association with Gleason score and high pathological stage	(Aboushousha et al., 2021)
	miR-410–3p	Tissue	Association with Gleason score >7, high grade and metastasis	(Y. Zhang et al., 2018)
	miR-548c-3p	Tissue	Association with high Gleason score	(Saffari et al., 2019)
	miR-572	Tissue	Higher miR expression in later stage disease is associated with Ki-67 protein higher and PTEN protein down	(Zang et al., 2021)
	miR-4534	Tissue	Upregulation is associated with high grade, high pathological stage, PSA recurrance and low survival	(Nip et al., 2016)
Local vs Metastatic	miR-148a, −152, and −200b	Blood	Association with metastasis by the silencing of PTEN via DNMT1	(Gurbuz et al., 2021)
	miR-214	Serum	Biomarker for bone metastasis (ROC AUC 0.955, CI 95 %: 0.872–1.000)	(Fang et al., 2019)
	miR-424	Blood	EVs-mediated release could promote disease recurrence and metastasis	(Albino et al., 2021)
Predictive				
Treatment response	miR-498	Cell lines	Induces radiation resistance in PCa cells	(Duan et al., 2019)
Drug response	miR-17 -18b, −20a, −20b, −92b	Cell lines	Resveratrol suppresses miRs expression and PTEN is restored	(Dhar et al., 2011)
	miRs-17, -20a, −106a, −106b	Cell lines	Resveratrol and pterostilbene downregulate miRs expression. Anticancer effect by restoring PTEN action	(Dhar et al., 2015)
	miR-21	Cell lines and animal model	The methylated urolithin A metabolite inhibits miR-21, anticancer effect by restoring PTEN action	(Zhou et al., 2016)
	miR-21	Cell lines	Its inhibition enhances the cytotoxicity effect of doxorubicin.	(Zhao et al., 2021)
	miR-503–5p	Cell lines and animal model	AG-490 can inhibit the growth of prostate cancer cells in a miR-dependent manner by targeting STAT3	(Tan et al., 2020)
	miR-572	Cell lines	Overexpression of miR-572 decreased sensitivity of PC cells to docetaxel treatment in a dose-dependent manner by reducing docetaxel-induced apoptosis.	(Zang et al., 2021)
Therapy	miR-20b	Cell lines	Knockdown shows an antitumor effect *in vitro*	(Guo et al., 2017)
	miR-21	Cell lines	Manipulation of miR-21 expression may be a possible means to improve the efficacy of IFN, alone or in combination with other chemotherapeutic agents.	(Yang et al., 2010)
	miR-21	Cell lines	GAS5 act as sponge of miR-21 and elevate the expression of PDCD4 and PTEN, key apoptosis regulators	(Zhu et al., 2019)
	miR-21	Cell lines and animal model	Peptide nucleic acids (PNA) anti-miR21 presents stability and therapeutic efficacy under *in vitro, ex vivo,* and *in vivo* conditions	(Kim et al., 2020)
	miR-26a, −92a	Cell lines	Its inhibition has an anticancer effect by increasing PTEN levels (1.46–3.03 fold).	(Tian et al., 2013)
	miR-92a	Cell lines	miR inhibition decreases proliferation, invasion, and migration, increases apoptosis	(Yanshen et al., 2021)
	miR-106a	Cell lines	miR inhibition decreases the proliferation and growth of cancer cells	(Lu et al., 2019)
	miR-146b	Cell lines	miR inhibition decreases cell proliferation via PTEN/AKT/mTOR by restoring autophagy	(Gao et al., 2018)
	miR-181a-5p	Cell lines	MBNL1-AS1 inhibits the progression of Pca (proliferation, invasion, and migration) via sponging miR-181a-5p and regulating PTEN/PI3K/AKT/mTOR pathway.	(Ding et al., 2021)
	miR-616	Cell lines and animal model	circRNA hsa_circ_0007494 functioned as a "molecular sponge" for miR-616 and hence upregulated PTEN.	(S. Zhang et al., 2020)
	miR-4534	Cell lines and animal model	Knockdown of miR-4534 impaired cell proliferation, migration/invasion and induced G0/G1 cell cycle arrest and apoptosis	(Nip et al., 2016)

AUC: Area under the curve; BPH: Bening prostate hyperplasia; CI: Confidence interval; EV: Extracellular vesicles; HC: Healthy control; PCa: Prostate cancer; ROC: Receiver Operating Characteristic.

chemoresistance. Additionally, the deregulated expression of miRNAs plays a fundamental role in resistance to major treatments in PCa which include androgen deprivation therapies, radiotherapy, and chemotherapy. Therefore, circulating miRNAs can be used as an alternative diagnostic and prognostic tool for PCa [51]. In Table 2, we summarized a list of candidate miRNAs and their clinical application in PCa.

One of the main advantages of the use of miRNAs as diagnostic biomarkers is their availability in biological fluids, such as the case of miR-21, 34c, −141, −148a, −152, and −275, which have been reported as useful in the discrimination between PCa of patients without cancer after obtaining a venipuncture sample [26,47]. However, the first stage in the investigation of new biomarkers involves the direct analysis of prostate tissue, where the overexpression of miR-548c-3p makes it a promising candidate to differentiate between PCa vs. matched adjacent non-cancerous tissues and benign prostatic hyperplasia (BPH) [52], like the miR-153 and -4534 [53,54].

The prognostic value of a biomarker collaborates with clinical practice for the benefit of the patient to follow up on the disease; analysis of miRNAs dysregulation and their target genes have provided evidence for the management of PCa, like miR-153, -410–3p, and −548c-3p, were associated with high Gleason score in PCa tissue, followed by a high pathological stage and metastasis. Their findings suggest that the upregulation of miRNAs resulted in the downregulation of PTEN, thereby activating the AKT/mTOR pathway [52,53,55]. Upregulation of miR-572 and -4534 is also related to the later-stage disease by directly binding to the PTEN 3′UTR, promoting proliferation, migration, and invasion of PCa cells [54,56]; moreover, miR-4534 was associated with biochemical recurrence and low survival [54].

Albino et al., reported EVs (extracellular vesicles)-mediated release of miR-424 can serve as an efficient means for transferring oncogenic signals across cells in the surrounding microenvironment and at distal metastatic sites promoting disease recurrence and progression. Furthermore, it was linked to aggressive tumor phenotypes, suggesting a role of this process in disease progression to metastatic and hormone-refractory PCa [57].

In PCa patients miR-148a, −152, and −200b serve as a prognosis circulating biomarker of metastasis [42], same as miR-214 with high specificity and sensitivity for distinguishing bone metastasis from local PCa, benign prostatic hyperplasia, and healthy control [58].

In PCa, aberrant expression of miRNAs correlates with resistance to radiotherapy, hormone therapy, and chemotherapy. A study by Duan et al. reported that miR-498 may affect radiotherapy efficacy by the inhibition of apoptosis, and the downregulation of miR-498 resulted in PCa cell survival after radiation treatment [59].

Regardless of drug response, resveratrol presents an anticancer effect by reversing the expression of PTEN by suppressing miR-17 -18b, −20a, −20b, and −92b expression [35] and pterostilbene exerts the same effect in those miRNAs, plus miR-106a and −106b [36]. Overexpression of miR-572 decreased the sensitivity of PCa cells to docetaxel treatment by reducing docetaxel-induced apoptosis, this suggests the expression level may be useful for predicting docetaxel response in PCa [56]. The miR-21 affects doxorubicin resistance, demonstrating that miR-21 inhibition increases the intracellular accumulation of doxorubicin, repressing permeability-glycoprotein activity and improving PTEN activity in the repression of the PI3K/AKT pathway [32]. A metabolite with potent inhibition action on miR-21 is methylated urolithin A, achieving antiproliferative effects by induction of cell death via PTEN and Pdcd4, suppressing the expression of AKT, b-catenin, and their downstream transcriptional factors, including c-Myc and MMP7 [30]. Also, AG-490 is suggested as a new drug candidate for the treatment of PCa, reducing miR-503–5p expression achieving STAT3 inhibition and PTEN upregulation [60].

The implication of specific miRNAs in several cellular pathways involved in PCa development and progression, together with the possibility of modifying their cellular expression levels, opened an exciting scenario for the medical management of this disease. The approaches for miRNA-based therapy on the PTEN pathway involved mainly the silencing of on-miRNAs. According to this, knockdown of miR-20b, −26a, −92a, −106a, −146b, and −4534 expression shows an antitumor effect *in vitro*, via PTEN/AKT/mTOR signaling pathway, decreasing cell proliferation, migration/invasion, and inducing apoptosis in PCa [39,41,45,54,61].

Recently, have been described some non-coding RNA molecules that act as “sponges” of miRNAs downregulated their expression [28,48,62] [23,43,58]. These are often RNA-based molecules, like Hsa_circ_0007494 targeting the miR-616 [62], MBNL1-AS1 (muscleblind-like 1 antisense RNA 1) sponge for miR-181a-5p [48] and GAS5, a lncRNA affecting the function of miR-21 [28]; in all of these cases decreased the abilities of cell proliferation, invasion, and migration via PTEN. Other molecules with high therapeutic potential are peptide nucleic acids (PNA), a study using PNA-anti miR21 demonstrated high stability and efficacy under *in vitro, ex vivo*, and *in vivo* treatment conditions, especially effective in preventing metastasis [31]. Also, miR-21 silencing enhances the apoptotic action of IFN, alone or in combination with other chemotherapeutic agents [25]. The findings suggested that the therapeutic efficacy of anti-miRNA depends on the type of modification and treatment conditions [31].

4. Discussion

MiRNAs are important regulators of gene expression and fundamental in the correct functioning of different molecular mechanisms and when changes in the expression of these, it is usually related to various pathologies [63]. Several mechanisms have been identified that can affect the gene expression of miRNAs, such as epigenetic changes related to the methylation of miRNA precursor genes. In the case of miR-200a and b, it has been observed that changes in the methylation of its promoter lead to a change in its gene expression being related to PCa [47]. This has been observed on other occasions, where various members of the miR-200 family, such as miR-200a and b, have shown changes in the methylation of their promoters, relating them to mechanisms such as the epithelial-mesenchymal transition in cancer due to changes in their gene expression [64,65]. Likewise, it was identified that another mechanism that could be relevant in the regulation of the expression of miRNAs is modifications in the activity of genes involved with their biogenesis, such as the Dicer and DGCR8 proteins that have been observed overexpressed in PCa, leading to an increase in the production of miRNAs [37,

40]. These results have been observed in other studies, where overexpression of the DGCR8 protein leads to an increase in the expression of miR-27a-3p [66]. Similarly, various authors have reported that changes in the expression of Dicer may be key in the regulation of the expression of various miRNAs, such as miR-124 and -144 in PCa [67]. Also, it has been observed that blocking the expression of Dicer excessively reduces the expression of MIR222HG, which shows that Dicer is key in its maturation [68].

The mechanisms may be responsible for the deregulation of different miRNAs in PCa. Different miRNAs with a possible relationship with PCa tumorigenesis have been reported. For example, miR-21, located on chromosome 17q23.2 in an intronic region of the TMEM49/VMP1 gene [69], has been one of the most reported and suggested miRNAs with a key role in PCa [26,31–33]. The most recent studies suggest that overexpression of miR-21 in PCa may be influenced by hypoxia in prostate tumors and suggest that this miRNA may have a very useful role as a diagnostic and prognostic biomarker in PCa [70]. Likewise, it has been observed that miR-21 overexpression can stimulate the production of PCa stem cells, which may be crucial in the pathogenesis of this pathology [71]. The miR-17 family has been widely reported for its implications in PCa [36,39–41]. The miR-17-92 cluster is located on chromosome 13q31.3 and encodes the miRs −17, −18a, −19a, −20a, −19b-1, -92a [69]. Recent studies suggest that some members of the miR-17 family, such as miR-20b, −106, and −17, are important regulators of members of the PI3K/AKT signaling pathway in PCa [72]. In this context, it has been observed that miR-20b is overexpressed in prostate tissue in patients with PCa, associating it with a poor prognosis and suggesting it is a promising biomarker in PCa. Likewise, it has been observed that miR-17, -20a, −20b, and −106a can distinguish between patients with high and low risk of developing aggressive PCa after radical prostatectomy, where overexpression of these confers a more aggressive phenotype [73]. These studies indicate that miRNAs are key in PCa tumorigenesis processes, which is mainly due to the genes that they can regulate, such as the PTEN tumor suppressor gene.

The deregulation of PTEN can be caused by a variety of genetic, epigenetic, and environmental factors. PTEN is a tumor suppressor

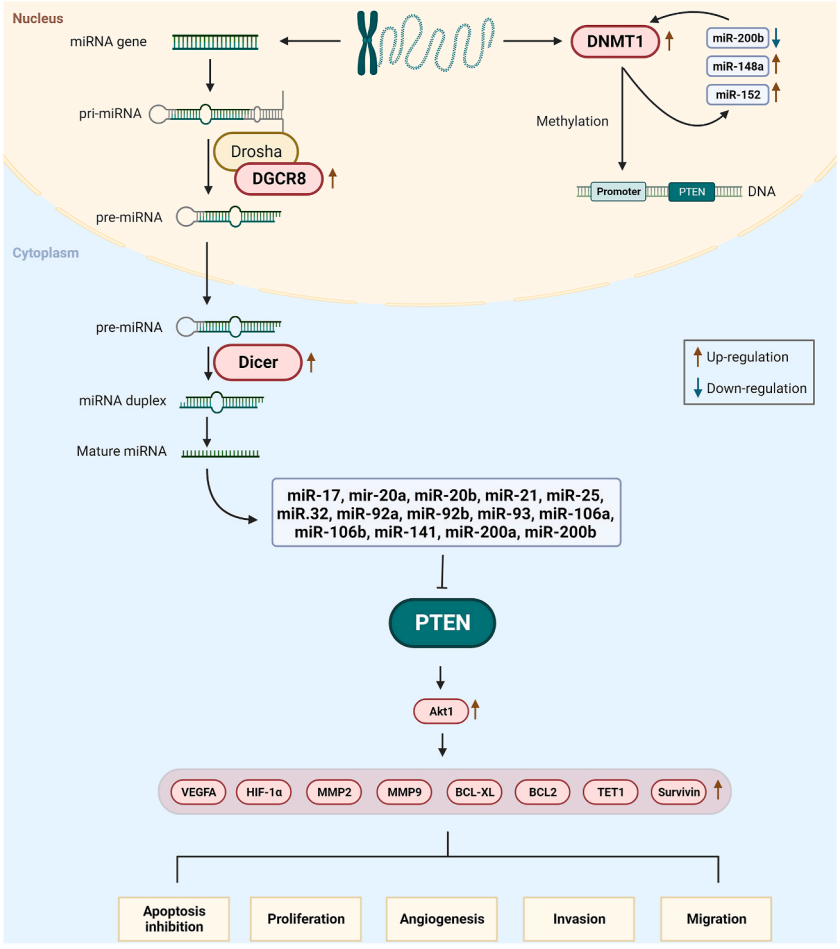


Fig. 3. Epigenetic regulation pathway of PTEN-miRNA mediated. Aberrant expression of microRNAs can lead to post-transcriptional silencing of PTEN. There are some mechanisms related to changes in the expression of miRNAs, for example, the overexpression of genes involved in their biogenesis can lead to their overproduction, as well as changes in DNA methylation caused by the overexpression of DNMT1. The mechanisms directly or indirectly impact the expression of PTEN, causing its silencing and in turn impact the PIK3/AKT pathway by promoting its expression and favoring the activation of involved genes. This, in turn, leads to important biological consequences, including the inhibition of apoptosis, proliferation, invasion, and cell migration.

gene that typically functions to inhibit uncontrolled cellular growth and maintain homeostasis in the PI3K/AKT/mTOR signaling pathway. When PTEN becomes deregulated, its function is compromised, which can contribute to the development of various diseases, including PCa [74,75]. One of the most direct causes of PTEN deregulation is genetic mutations. Mutations affecting the structure or function of the PTEN protein can lead to partial or complete loss of its tumor suppressor activity. These mutations can be inherited or acquired during a person's lifetime due to factors such as exposure to carcinogens [74,76]. A plethora of miRNAs have been identified to modulate PTEN expression at the post-transcriptional and reduce its expression through degradation or translation inhibition. These miRNAs include those that contain a single hairpin structure [10]. This is consistent with reports from several studies that have established the relationship between miRNAs in PTEN regulation [77–81].

One of the main miRNAs reported in the regulation of PTEN is the miR-21 and -17 family. This miRNA family negatively regulates the expression of PTEN by binding it to the 3′UTR region of PTEN mRNA. When members of the miR-21 or miR-17 family bind to this region, they hinder the translation of PTEN mRNA into protein or facilitate its degradation. As a result, the amount of available PTEN protein in the cell is reduced. Since PTEN typically functions as a tumor suppressor by inhibiting the PI3K/AKT/mTOR signaling pathway, the reduction in its expression due to negative regulation by these miRNAs can lead to the hyperactivation of this pathway. This can promote uncontrolled cell proliferation, cell survival, and resistance to apoptosis, which are characteristics associated with cancer and other related diseases. The miR-17 family can also influence other aspects of PTEN regulation. For example, it has been found that miR-20a can negatively regulate mitogen-activated protein kinase (MAPK) and phosphatase 3 (DUSP6), which in turn can affect the PTEN signaling pathway [25–41].

It is important to note that miRNAs bind preferentially to 3′UTR regions because they contain complementary binding sites for miRNAs. When a miRNA binds to this region, it can have two main effects on gene expression, namely inhibition of translation and mRNA degradation [82].

On the other hand, when PTEN is deregulated, several regulatory cascades are affected. The most significant and related one is the PI3K/AKT pathway. PTEN functions as a negative regulator, overseeing the pathway's activity. When PTEN is functional, it inhibits AKT activation, thereby controlling cell growth, survival, and proliferation. However, if PTEN is mutated or downregulated, AKT becomes hyperactivated, resulting in uncontrolled cell division and contributing to diseases like cancer [27,29,37,44,46,48,49]. Molecularly, PTEN's deregulation disrupts the balance between cell growth and suppression. The sustained activation of AKT drives aberrant cellular behaviors, fostering tumor development. Additionally, PI3K activation triggers heightened PTEN translation, which acts against the pathway's pro-growth impact. This harmonious interplay between PI3K and PTEN maintains cellular equilibrium. Disruption of this balance can contribute to diseases such as cancer, underscoring the importance of this regulatory interconnection [10,74,75]. Clinically, PTEN's impact on the PI3K/AKT pathway has significant implications [48]. Hyperactivation of this pathway due to PTEN loss contributes to cancer progression, drug resistance, and poor prognosis. Understanding these molecular changes informs therapeutic strategies aimed at targeting the PI3K/AKT pathway in various cancers, offering potential avenues for treatment and personalized medicine approaches.

Based on these findings, the main epigenetic mechanisms responsible for the deregulation of PTEN gene expression are proposed in this systematic study. It is highlighted that this dysregulation leads to important biological consequences, including inhibition of apoptosis, proliferation, invasion, and cell migration (Fig. 3). Therefore, this study represents the first comprehensive review of PTEN gene regulation mediated by epigenetic mechanisms, specifically through miRNAs.

5. Conclusion

Altered miRNA expression plays a pivotal role in PCa pathogenesis. According to our review miR-21 and members of the miR-17 family (miR-20a, −20b, −93, −106a, and −106b), are the most altered and reviewed miRNAs in PCa-associated with PTEN dysregulation. The downregulation of PTEN mediated by miRNAs promotes hyperactivation of the PI3K/AKT/mTOR pathway, and interactions with intermediary genes support the inhibition of apoptosis, angiogenesis, proliferation, invasion, and metastasis. Moreover, miRNAs could affect PCa responses to various treatment strategies including radio, and chemotherapy. Thus, its modulation can reduce resistance to chemotherapy, and radiation therapy mostly by restoring PTEN activity. Hence, miRNAs are clinically valuable biomarkers for diagnosis, prognostic, and therapeutic targets.

Some limitations need to be considered. First, we included only published studies found in major electronic databases, which could have biased the body of evidence because of the exclusion of gray literature. Second, we included only studies published in English and Spanish, which could cause a language bias because some important studies are not published in peer-reviewed journals in these languages. Third, some studies analyzed showed limited descriptions of the materials and methods, thus representing a performance bias for assessing the quality of the research.

CRediT authorship contribution statement

Fernando Bergez-Hernández: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **Martín Irigoyen-Arredondo:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **Alejandra Martínez-Camberos:** Conceptualization, Formal analysis, Investigation, Supervision, Visualization, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We acknowledge the support provided by the *Programa del Apoyo al Fortalecimiento de la Investigación y el Posgrado* from Universidad Autónoma de Occidente in carrying out this research.

References

[1] J. Li, C. Yen, D. Liaw, K. Podsypanina, S. Bose, S.I. Wang, J. Puc, C. Miliaresis, L. Rodgers, R. McCombie, S.H. Bigner, B.C. Giovanella, M. Ittmann, B. Tycko, H. Hibshoosh, M.H. Wigler, R. Parsons, *PTEN* , a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer, Science 275 (1997) 1943–1947, https://doi.org/10.1126/science.275.5308.1943.
[2] M.S. Song, L. Salmena, P.P. Pandolfi, The functions and regulation of the PTEN tumour suppressor, Nat. Rev. Mol. Cell Biol. 13 (2012) 283–296, https://doi.org/10.1038/nrm3330.
[3] N. Chalhoub, S.J. Baker, PTEN and the PI3-kinase pathway in cancer, Annu. Rev. Pathol. 4 (2009) 127–150, https://doi.org/10.1146/annurev.pathol.4.110807.092311.
[4] T. Maehama, J.E. Dixon, The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate, J. Biol. Chem. 273 (1998) 13375–13378, https://doi.org/10.1074/jbc.273.22.13375.
[5] V. Stambolic, A. Suzuki, J.L. de la Pompa, G.M. Brothers, C. Mirtsos, T. Sasaki, J. Ruland, J.M. Penninger, D.P. Siderovski, T.W. Mak, Negative regulation of PKB/Akt-Dependent cell survival by the tumor suppressor PTEN, Cell 95 (1998) 29–39, https://doi.org/10.1016/S0092-8674(00)81780-8.
[6] L. Salmena, A. Carracedo, P.P. Pandolfi, Tenets of PTEN tumor suppression, Cell 133 (2008) 403–414, https://doi.org/10.1016/j.cell.2008.04.013.
[7] X. Wang, H. Huang, K.H. Young, The PTEN tumor suppressor gene and its role in lymphoma pathogenesis, Aging 7 (2015) 1032–1049, https://doi.org/10.18632/aging.100855.
[8] V. Álvarez-Garcia, Y. Tawil, H.M. Wise, N.R. Leslie, Mechanisms of PTEN loss in cancer: it's all about diversity, Semin. Cancer Biol. 59 (2019) 66–79, https://doi.org/10.1016/j.semcancer.2019.02.001.
[9] W. Li, T. Zhang, L. Guo, L. Huang, Regulation of PTEN expression by noncoding RNAs, J. Exp. Clin. Cancer Res. 37 (2018) 223, https://doi.org/10.1186/s13046-018-0898-9.
[10] M. Bermúdez Brito, Focus on PTEN regulation, Front. Oncol. 5 (2015), https://doi.org/10.3389/fonc.2015.00166.
[11] S. Ghafouri-Fard, A. Abak, H. Shoorei, M. Mohaqiq, J. Majidpoor, A. Sayad, M. Taheri, Regulatory role of microRNAs on PTEN signaling, Biomed. Pharmacother. 133 (2021) 110986, https://doi.org/10.1016/j.biopha.2020.110986.
[12] F. Bergez-Hernández, E. Arámbula-Meraz, M. Alvarez-Arrazola, M. Irigoyen-Arredondo, F. Luque-Ortega, A. Martínez-Camberos, D. Cedano-Prieto, J. Contreras-Gutiérrez, C. Martínez-Valenzuela, N. García-Magallanes, Expression analysis of miRNAs and their potential role as biomarkers for prostate cancer detection, Am. J. Men's Health 16 (2022), https://doi.org/10.1177/15579883221120989.
[13] A. Chakrabortty, D.J. Patton, B.F. Smith, P. Agarwal, miRNAs: potential as biomarkers and therapeutic targets for cancer, Genes 14 (2023) 1375, https://doi.org/10.3390/genes14071375.
[14] F. Ghamlouche, A. Yehya, Y. Zeid, H. Fakhereddine, J. Fawaz, Y.-N. Liu, M. Al-Sayegh, W. Abou-Kheir, MicroRNAs as clinical tools for diagnosis, prognosis, and therapy in prostate cancer, Transl. Oncol. 28 (2023) 101613, https://doi.org/10.1016/j.tranon.2022.101613.
[15] H.N. Luu, H.-Y. Lin, K.D. Sørensen, O.O. Ogunwobi, N. Kumar, G. Chornokur, C. Phelan, D. Jones, L. Kidd, J. Batra, K. Yamoah, A. Berglund, R.J. Rounbehler, M. Yang, S.H. Lee, N. Kang, S.J. Kim, J.Y. Park, G. Di Pietro, miRNAs associated with prostate cancer risk and progression, BMC Urol. 17 (2017) 18, https://doi.org/10.1186/s12894-017-0206-6.
[16] N.R. Leslie, M. Foti, Non-genomic loss of PTEN function in cancer: not in my genes, Trends Pharmacol. Sci. 32 (2011) 131–140, https://doi.org/10.1016/j.tips.2010.12.005.
[17] L. Wan, Y. Wang, J. Li, Y. Wang, H. Zhang, Inhibition of the AKT/mTOR pathway negatively regulates PTEN expression via miRNAs, Acta Biochim. Biophys. Sin. 54 (2022) 1637–1647, https://doi.org/10.3724/abbs.2022159.
[18] C. Porta, C. Paglino, A. Mosca, Targeting PI3K/Akt/mTOR signaling in cancer, Front. Oncol. 4 (2014), https://doi.org/10.3389/fonc.2014.00064.
[19] N.M. McLoughlin, C. Mueller, T.N. Grossmann, The therapeutic potential of PTEN modulation: targeting strategies from gene to protein, Cell Chem. Biol. 25 (2018) 19–29, https://doi.org/10.1016/j.chembiol.2017.10.009.
[20] D.J. Turnham, N. Bullock, M.S. Dass, J.N. Staffurth, H.B. Pearson, The PTEN conundrum: how to target PTEN-deficient prostate cancer, Cells 9 (2020) 2342, https://doi.org/10.3390/cells9112342.
[21] E. Sellars, M. Gabra, L. Salmena, The complex landscape of *PTEN* mRNA regulation, Cold Spring Harb. Perspect. Med. 10 (2020) a036236, https://doi.org/10.1101/cshperspect.a036236.
[22] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, R. Chou, J. Glanville, J. M. Grimshaw, A. Hróbjartsson, M.M. Lalu, T. Li, E.W. Loder, E. Mayo-Wilson, S. McDonald, L.A. McGuinness, L.A. Stewart, J. Thomas, A.C. Tricco, V.A. Welch, P. Whiting, D. Moher, The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, BMJ 372 (2021) n71, https://doi.org/10.1136/bmj.n71.
[23] C.R. Hooijmans, M.M. Rovers, R.B. de Vries, M. Leenaars, M. Ritskes-Hoitinga, M.W. Langendam, SYRCLE's risk of bias tool for animal studies, BMC Med. Res. Methodol. 14 (2014) 43, https://doi.org/10.1186/1471-2288-14-43.
[24] CASP Referencing & Creative Commons Licence, CASP - Crit. Apprais. Ski. Programme (n.d.). https://casp-uk.net/referencing/ (accessed April 19, 2023).
[25] C.H. Yang, J. Yue, M. Fan, L.M. Pfeffer, Interferon induces miR-21 through a STAT3-dependent pathway as a suppressive negative feedback on interferon-induced apoptosis, Cancer Res. 70 (2010) 8108–8116, https://doi.org/10.1158/0008-5472.CAN-10-2579.
[26] P. Kshirsagar, P. Seshacharyulu, S. Muniyan, S. Rachagani, L.M. Smith, C. Thompson, A. Shah, K. Mallya, S. Kumar, M. Jain, S.K. Batra, DNA-gold nanoprobe-based integrated biosensing technology for non-invasive liquid biopsy of serum miRNA: a new frontier in prostate cancer diagnosis, Nanomed. Nanotechnol. Biol. Med. 43 (2022), https://doi.org/10.1016/j.nano.2022.102566.
[27] L.-Z. Liu, C. Li, Q. Chen, Y. Jing, R. Carpenter, Y. Jiang, H.-F. Kung, L. Lai, B.-H. Jiang, Mir-21 induced angiogenesis through AKT and ERK activation and HIF-1α expression, PLoS One 6 (2011), https://doi.org/10.1371/journal.pone.0019139.
[28] L. Zhu, Q. Zhu, H. Wen, X. Huang, G. Zheng, Mutations in GAS5 affect the transformation from benign prostate proliferation to aggressive prostate cancer by affecting the transcription efficiency of GAS5, J. Cell. Physiol. 234 (2019) 8928–8940, https://doi.org/10.1002/jcp.27561.
[29] Y. Yang, J.-X. Guo, Z.-Q. Shao, miR-21 targets and inhibits tumor suppressor gene PTEN to promote prostate cancer cell proliferation and invasion: an experimental study, Asian Pac. J. Tropical Med. 10 (2017) 87–91, https://doi.org/10.1016/j.apjtm.2016.09.011.
[30] B. Zhou, J. Wang, G. Zheng, Z. Qiu, Methylated urolithin A, the modified ellagitannin-derived metabolite, suppresses cell viability of DU145 human prostate cancer cells via targeting miR-21, Food Chem. Toxicol. 97 (2016) 375–384, https://doi.org/10.1016/j.fct.2016.10.005.
[31] K. Kim, H.H. Kim, C.-H. Lee, S. Kim, G.J. Cheon, K.W. Kang, J.-K. Chung, H. Youn, Therapeutic efficacy of modified anti-miR21 in metastatic prostate cancer, Biochem. Biophys. Res. Commun. 529 (2020) 707–713, https://doi.org/10.1016/j.bbrc.2020.05.215.

[32] W. Zhao, L. Ning, L. Wang, T. Ouyang, L. Qi, R. Yang, Y. Wu, miR-21 inhibition reverses doxorubicin-resistance and inhibits PC3 human prostate cancer cells proliferation, Andrologia 53 (2021), https://doi.org/10.1111/and.14016.

[33] M.M. Khan, M.T. Mohsen, M.Z. Malik, S.A. Bagabir, M.F. Alkhanani, S. Haque, M. Serajuddin, M. Bharadwaj, Identification of potential key genes in prostate cancer with gene expression, pivotal pathways and regulatory networks analysis using integrated bioinformatics methods, Genes 13 (2022), https://doi.org/10.3390/genes13040655.

[34] M. Folini, P. Gandellini, N. Longoni, V. Profumo, M. Callari, M. Pennati, M. Colecchia, R. Supino, S. Veneroni, R. Salvioni, R. Valdagni, M.G. Daidone, N. Zaffaroni, miR-21: an oncomir on strike in prostate cancer, Mol. Cancer 9 (2010), https://doi.org/10.1186/1476-4598-9-12.

[35] S. Dhar, C. Hicks, A.S. Levenson, Resveratrol and prostate cancer: promising role for microRNAs, Mol. Nutr. Food Res. 55 (2011) 1219–1229, https://doi.org/10.1002/mnfr.201100141.

[36] S. Dhar, A. Kumar, A.M. Rimando, X. Zhang, A.S. Levenson, Resveratrol and pterostilbene epigenetically restore PTEN expression by targeting oncomiRs of the miR-17 family in prostate cancer, Oncotarget 6 (2015) 27214–27226.

[37] L. Poliseno, L. Salmena, L. Riccardi, A. Fornari, M.S. Song, R.M. Hobbs, P. Sportoletti, S. Varmeh, A. Egia, G. Fedele, L. Rameh, M. Loda, P.P. Pandolfi, Identification of the miR-106b~25 microRNA cluster as a proto-oncogenic PTEN-targeting intron that cooperates with its host gene MCM7 in transformation, Sci. Signal. 3 (2010), https://doi.org/10.1126/scisignal.2000594.

[38] G. Wang, A. Lunardi, J. Zhang, Z. Chen, U. Ala, K.A. Webster, Y. Tay, E. Gonzalez-Billalabeitia, A. Egia, D.R. Shaffer, B. Carver, X.-S. Liu, R. Taulli, W.P. Kuo, C. Nardella, S. Signoretti, C. Cordon-Cardo, W.L. Gerald, P.P. Pandolfi, Zbtb7a suppresses prostate cancer through repression of a Sox9-dependent pathway for cellular senescence bypass and tumor invasion, Nat. Genet. 45 (2013) 739–746, https://doi.org/10.1038/ng.2654.

[39] J. Guo, Z. Xiao, X. Yu, R. Cao, miR-20b promotes cellular proliferation and migration by directly regulating phosphatase and tensin homolog in prostate cancer, Oncol. Lett. 14 (2017) 6895–6900, https://doi.org/10.3892/ol.2017.7041.

[40] C.D. Belair, A. Paikari, F. Moltzahn, A. Shenoy, C. Yau, M. Dall'Era, J. Simko, C. Benz, R. Blelloch, DGCR8 is essential for tumor progression following PTEN loss in the prostate, EMBO Rep. 16 (2015) 1219–1232, https://doi.org/10.15252/embr.201439925.

[41] J.I. Lu, X. Mu, Q. Yin, K. Hu, MiR-106a contributes to prostate carcinoma progression through PTEN, Oncol. Lett. 17 (2019) 1327–1332, https://doi.org/10.3892/ol.2018.9697.

[42] J. Li, X. Yang, H. Guan, A. Mizokami, E.T. Keller, X. Xu, X. Liu, J. Tan, L. Hu, Y. Lu, J. Zhang, Exosome-derived microRNAs contribute to prostate cancer chemoresistance, Int. J. Oncol. 49 (2016) 838–846, https://doi.org/10.3892/ijo.2016.3560.

[43] L. Latonen, M. Scaravilli, A. Gillen, S. Hartikainen, F.-P. Zhang, P. Ruusuvuori, P. Kujala, M. Poutanen, T. Visakorpi, In vivo expression of miR-32 induces proliferation in prostate epithelium, Am. J. Pathol. 187 (2017) 2546–2557, https://doi.org/10.1016/j.ajpath.2017.07.012.

[44] L. Tian, Y.X. Fang, J.L. Xue, J.Z. Chen, Four microRNAs promote prostate cell proliferation with regulation of PTEN and its downstream signals in vitro, PLoS One 8 (2013), https://doi.org/10.1371/journal.pone.0075885.

[45] Z. Yanshen, Y. Lifen, W. Xilian, D. Zhong, M. Huihong, miR-92a promotes proliferation and inhibits apoptosis of prostate cancer cells through the PTEN/Akt signaling pathway, Libyan J. Med. 16 (2021), https://doi.org/10.1080/19932820.2021.1971837.

[46] N.H. Farina, A. Zingiryan, J.A. Akech, C.J. Callahan, H. Lu, J.L. Stein, L.R. Languino, G.S. Stein, J.B. Lian, A microRNA/Runx1/Runx2 network regulates prostate tumor progression from onset to adenocarcinoma in TRAMP mice, Oncotarget 7 (2016) 70462–70474, https://doi.org/10.18632/oncotarget.11992.

[47] V. Gurbuz, S. Sozen, C.Y. Bilen, E. Konac, miR-148a, miR-152 and miR-200b promote prostate cancer metastasis by targeting DNMT1 and PTEN expression, Oncol. Lett. 22 (2021), https://doi.org/10.3892/ol.2021.13066.

[48] X. Ding, X. Xu, X.-F. He, Y. Yuan, C. Chen, X.-Y. Shen, S. Su, Z. Chen, S.-T. Xu, Y.-H. Huang, Muscleblind-like 1 antisense RNA 1 inhibits cell proliferation, invasion, and migration of prostate cancer by sponging miR-181a-5p and regulating PTEN/PI3K/AKT/mTOR signaling., Bioengineered 12 (n.d.) 803–814. https://doi.org/10.1080/21655979.2021.1890383.

[49] N.N.O. Ngalame, E.J. Tokar, R.J. Person, Y. Xu, M.P. Waalkes, Aberrant microRNA expression likely controls RAS oncogene activation during malignant transformation of human prostate epithelial and stem cells by arsenic, Toxicol. Sci. 138 (2014) 268–277, https://doi.org/10.1093/toxsci/kfu002.

[50] A. Takao, K. Yoshikawa, S. Karnan, A. Ota, H. Uemura, M.A. De Velasco, Y. Kura, S. Suzuki, R. Ueda, T. Nishino, Y. Hosokawa, Generation of PTEN-knockout (-/-) murine prostate cancer cells using the CRISPR/Cas9 system and comprehensive gene expression profiling, Oncol. Rep. 40 (2018) 2455–2466, https://doi.org/10.3892/or.2018.6683.

[51] C.E. Condrat, D.C. Thompson, M.G. Barbu, O.L. Bugnar, A. Boboc, D. Cretoiu, N. Suciu, S.M. Cretoiu, S.C. Voinea, miRNAs as biomarkers in disease: latest findings regarding their role in diagnosis and prognosis, Cells 9 (2020) 276, https://doi.org/10.3390/cells9020276.

[52] M. Saffari, S.M.H. Ghaderian, M.D. Omrani, M. Afsharpad, K. Shankaie, N. Samadaian, The association of miR-let 7b and miR-548 with PTEN in prostate cancer, Urol. J. 16 (2019) 267–273, https://doi.org/10.22037/uj.v0i0.4564.

[53] T. Aboushousha, E.I. El-Nahas, A. El-Hindawi, D. Elwi, H. El-Ganzouri, O. Hammam, M. Magdy, N.S. Helal, Implication of miRNA-153 on PTEN expression in prostatic adenocarcinoma, Eur. Rev. Med. Pharmacol. Sci. 25 (2021) 6834–6843, https://doi.org/10.26355/eurrev_202111_27231.

[54] H. Nip, A.A. Dar, S. Saini, M. Colden, S. Varahram, H. Chowdhary, S. Yamamura, Y. Mitsui, Y. Tanaka, T. Kato, Y. Hashimoto, M. Shiina, P. Kulkarni, P. Dasgupta, M. Imai-Sumida, Z.L. Tabatabai, K. Greene, G. Deng, R. Dahiya, S. Majid, Oncogenic microRNA-4534 regulates PTEN pathway in prostate cancer, Oncotarget 7 (2016) 68371–68384, https://doi.org/10.18632/oncotarget.12031.

[55] Y. Zhang, D. Zhang, J. Lv, S. Wang, Q. Zhang, miR-410-3p promotes prostate cancer progression via regulating PTEN/AKT/mTOR signaling pathway, Biochem. Biophys. Res. Commun. 503 (2018) 2459–2465, https://doi.org/10.1016/j.bbrc.2018.06.176.

[56] M. Zang, X. Guo, M. Chen, The role of microRNA-572 in the proliferation and chemotherapeutic treatment of prostate cancer, J. Int. Med. Res. 49 (2021), https://doi.org/10.1177/03000605211014363.

[57] D. Albino, M. Falcione, V. Uboldi, D.O. Temilola, G. Sandrini, J. Merulla, G. Civenni, A. Kokanovic, A. Stürchler, D. Shinde, M. Garofalo, R.P. Mestre, V. Constâncio, M. Wium, J. Burrello, N. Baranzini, A. Grimaldi, J.-P. Theurillat, D. Bossi, L. Barile, R.M. Henrique, C. Jeronimo, L.F. Zerbini, C.V. Catapano, G. M. Carbone, Circulating extracellular vesicles release oncogenic miR-424 in experimental models and patients with aggressive prostate cancer, Commun. Biol. 4 (2021) 119, https://doi.org/10.1038/s42003-020-01642-5.

[58] Y. Fang, J. Qiu, Z.-B. Jiang, S.-R. Xu, Z.-H. Zhou, R.-L. He, Increased serum levels of miR-214 in patients with PCa with bone metastasis may serve as a potential biomarker by targeting PTEN, Oncol. Lett. 17 (2019) 398–405, https://doi.org/10.3892/ol.2018.9522.

[59] X.-M. Duan, X.-N. Liu, Y.-X. Li, Y.-Q. Cao, A. Silayiding, R.-K. Zhang, J.-P. Wang, MicroRNA-498 promotes proliferation, migration, and invasion of prostate cancer cells and decreases radiation sensitivity by targeting PTEN, Kaohsiung J. Med. Sci. 35 (2019) 659–671, https://doi.org/10.1002/kjm2.12108.

[60] G. Tan, L. Jiang, G. Li, K. Bai, ESTAT3 inhibitor AG-490 inhibits the growth of prostate cancer by miR-503-5p both in vivo and in vitro, Technol. Cancer Res. Treat. 19 (2020), https://doi.org/10.1177/1533033820948062.

[61] S. Gao, Z. Zhao, R. Wu, L. Wu, X. Tian, Z. Zhang, MiR-146b inhibits autophagy in prostate cancer by targeting the PTEN/Akt/mTOR signaling pathway, Aging 10 (2018) 2113–2121, https://doi.org/10.18632/aging.101534.

[62] S. Zhang, X. Zhang, G. Chen, X. Zheng, X. Zhu, L. Shan, Hsa_circ_0007494 suppresses prostate cancer progression via miR-616/PTEN axis, Exp. Cell Res. 395 (2020), https://doi.org/10.1016/j.yexcr.2020.112233.

[63] E. Arámbula-Meraz, F. Bergez-Hernández, E. Leal-León, E. Romo-Martínez, V. Picos-Cárdenas, F. Luque-Ortega, J. Romero-Quintana, M. Alvarez-Arrazola, N. García-Magallanes, Expression of miR-148b-3p is correlated with overexpression of biomarkers in prostate cancer, Genet. Mol. Biol. 43 (2020) e20180330, https://doi.org/10.1590/1678-4685-GMB-2018-0330.

[64] M. Mancini, M. Grasso, L. Muccillo, F. Babbio, F. Precazzini, I. Castiglioni, V. Zanetti, F. Rizzo, C. Pistore, M.G. De Marino, M. Zocchi, V. Del Vescovo, V. Licursi, G. Giurato, A. Weisz, P. Chiarugi, L. Sabatino, M.A. Denti, I.M. Bonapace, DNMT3A epigenetically regulates key microRNAs involved in epithelial-to-mesenchymal transition in prostate cancer, Carcinogenesis 42 (2021) 1449–1460, https://doi.org/10.1093/carcin/bgab101.

[65] V. Davalos, C. Moutinho, A. Villanueva, R. Boque, P. Silva, F. Carneiro, M. Esteller, Dynamic epigenetic regulation of the microRNA-200 family mediates epithelial and mesenchymal transitions in human tumorigenesis, Oncogene 31 (2012) 2062–2074, https://doi.org/10.1038/onc.2011.383.

[66] D. Long, L. Xu, Z. Deng, D. Guo, Y. Zhang, Z. Liu, C. Zhang, HPV16 E6 enhances the radiosensitivity in HPV-positive human head and neck squamous cell carcinoma by regulating the miR-27a-3p/SMG1 axis, Infect. Agents Cancer 16 (2021) 56, https://doi.org/10.1186/s13027-021-00397-w.
[67] H. Gu, M. Liu, C. Ding, X. Wang, R. Wang, X. Wu, R. Fan, Hypoxia-responsive miR-124 and miR-144 reduce hypoxia-induced autophagy and enhance radiosensitivity of prostate cancer cells via suppressing PIM1, Cancer Med. 5 (2016) 1174–1182, https://doi.org/10.1002/cam4.664.
[68] J. Sun, S. Li, F. Wang, C. Fan, J. Wang, Identification of key pathways and genes in PTEN mutation prostate cancer by bioinformatics analysis, BMC Med. Genet. 20 (2019) 191, https://doi.org/10.1186/s12881-019-0923-7.
[69] J. Rhim, W. Baek, Y. Seo, J.H. Kim, From molecular mechanisms to therapeutics: understanding MicroRNA-21 in cancer, Cells 11 (2022) 2791, https://doi.org/10.3390/cells11182791.
[70] C.Z. Angel, M.Y.C. Stafford, C.J. McNally, H. Nesbitt, D.J. McKenna, MiR-21 is induced by hypoxia and down-regulates RHOB in prostate cancer, Cancers 15 (2023) 1291, https://doi.org/10.3390/cancers15041291.
[71] K.K. Shukla, G.R. Choudhary, S. Sankanagoudar, S. Misra, J.R. Vishnoi, P. Pareek, K.K. Pilla, S.N. Pandey, P. Sharma, Deregulation of miR-10b and miR-21 correlate with cancer stem cells expansion through the apoptotic pathway in prostate cancer, Asian Pac. J. Cancer Prev. APJCP 24 (2023) 2105–2119, https://doi.org/10.31557/APJCP.2023.24.6.2105.
[72] M. Wiesehöfer, E.D. Czyrnik, M. Spahn, S. Ting, H. Reis, J.T. Dankert, G. Wennemuth, Increased expression of AKT3 in neuroendocrine differentiated prostate cancer cells alters the response towards anti-androgen treatment, Cancers 13 (2021) 578, https://doi.org/10.3390/cancers13030578.
[73] C. Hoey, M. Ahmed, A. Fotouhi Ghiam, D. Vesprini, X. Huang, K. Commisso, A. Commisso, J. Ray, E. Fokas, D.A. Loblaw, H.H. He, S.K. Liu, Circulating miRNAs as non-invasive biomarkers to predict aggressive prostate cancer after radical prostatectomy, J. Transl. Med. 17 (2019) 173, https://doi.org/10.1186/s12967-019-1920-5.
[74] N. Fusco, E. Sajjadi, K. Venetis, G. Gaudioso, G. Lopez, C. Corti, E. Guerini Rocco, C. Criscitiello, U. Malapelle, M. Invernizzi, PTEN alterations and their role in cancer management: are we making headway on precision medicine? Genes 11 (2020) 719, https://doi.org/10.3390/genes11070719.
[75] R. Mukherjee, K.G. Vanaja, J.A. Boyer, S. Gadal, H. Solomon, S. Chandarlapaty, A. Levchenko, N. Rosen, Regulation of PTEN translation by PI3K signaling maintains pathway homeostasis, Mol. Cell 81 (2021) 708–723.e5, https://doi.org/10.1016/j.molcel.2021.01.033.
[76] M. Cully, H. You, A.J. Levine, T.W. Mak, Beyond PTEN mutations: the PI3K pathway as an integrator of multiple inputs during tumorigenesis, Nat. Rev. Cancer 6 (2006) 184–192, https://doi.org/10.1038/nrc1819.
[77] P.T. Jindra, J. Bagley, J.G. Godwin, J. Iacomini, Costimulation-dependent expression of MicroRNA-214 increases the ability of T cells to proliferate by targeting *pten*, J. Immunol. 185 (2010) 990–997, https://doi.org/10.4049/jimmunol.1000793.
[78] P. Mu, Y.-C. Han, D. Betel, E. Yao, M. Squatrito, P. Ogrodowski, E. De Stanchina, A. D'Andrea, C. Sander, A. Ventura, Genetic dissection of the *miR-17~92* cluster of microRNAs in Myc-induced B-cell lymphomas, Genes Dev. 23 (2009) 2806–2811, https://doi.org/10.1101/gad.1872909.
[79] V. Olive, M.J. Bennett, J.C. Walker, C. Ma, I. Jiang, C. Cordon-Cardo, Q.-J. Li, S.W. Lowe, G.J. Hannon, L. He, *miR-19* is a key oncogenic component of *mir-17-92*, Genes Dev. 23 (2009) 2839–2849, https://doi.org/10.1101/gad.1861409.
[80] B. Wang, S. Majumder, G. Nuovo, H. Kutay, S. Volinia, T. Patel, T.D. Schmittgen, C. Croce, K. Ghoshal, S.T. Jacob, Role of microRNA-155 at early stages of hepatocarcinogenesis induced by choline-deficient and amino acid-defined diet in C57BL/6 mice, Hepatology 50 (2009) 1152–1161, https://doi.org/10.1002/hep.23100.
[81] C. Xiao, L. Srinivasan, D.P. Calado, H.C. Patterson, B. Zhang, J. Wang, J.M. Henderson, J.L. Kutok, K. Rajewsky, Lymphoproliferative disease and autoimmunity in mice with increased miR-17-92 expression in lymphocytes, Nat. Immunol. 9 (2008) 405–414, https://doi.org/10.1038/ni1575.
[82] Y. Hoffman, D.R. Bublik, A.P. Ugalde, R. Elkon, T. Biniashvili, R. Agami, M. Oren, Y. Pilpel, 3'UTR shortening potentiates MicroRNA-based repression of pro-differentiation genes in proliferating human cells, PLoS Genet. 12 (2016) e1005879, https://doi.org/10.1371/journal.pgen.1005879.