University of Cyprus
Department of Biological Sciences

The nexus between circRNA and prostate cancer from the complex interventions to treatment expectation

Ahmad Alshikh Saleh

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ABSTRACT

Circular RNAs (circRNAs) are a kind of RNA that results through a non-regular process known as alternative splicing. Because of their possible regulatory activities during gene expression, circRNAs have lately sparked attention in transcriptome research. CircRNAs can operate as microRNA sponges, influencing transcription as a result of their intricate engagement in normal transcriptional processes. Some early studies have showed that circRNAs play important roles in human disorders, including cancer. As the statistical association between PC and circRNAs grows, genetic and environmental studies are being built to investigate the possible targets of circRNAs in preventing carcinogenesis. Despite the fact that the association between circRNAs and PCs is well established, the integrated signaling pathways and molecular mechanisms of circRNA-modulated gene regulation are yet unknown. this research includes the latest development and research linking circRNAs to prostate cancer.

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COMPOSITION OF THE EXAMINATION COMMITTEE

Thesis Supervisor (Examination Committee coordinator): Dr. Anna Charalambous, STS, Dept. of Biological Sciences, UCY

Committee Member: Prof. Leondios Kostrikis, Dept. of Biological Sciences, UCY

Committee Member: Assoc. Prof. Paris Skourides, Dept. of Biological Sciences, UCY

SEMINAR ANNOUNCEMENT

University of Cyprus
Department of Biological Sciences

BIO 680 Scientific Methodology in Molecular Biology

Student Presentation

Tuesday, 03 May 2022 at 11:00 am
Building ΘΕΕ02, Room B172, Panepistimioupoli Campus

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Ahmad Alshikh Saleh

Thesis Supervisor: Special Teaching Staff, Dr. Annita Charalambous

"The nexus between circRNA and prostate cancer from the complex interventions to treatment expectation"

Circular RNAs (circRNAs) are a kind of RNA that results through a non-regular process known as alternative splicing. Because of their possible regulatory activities during gene expression, circRNAs have lately sparked attention in transcriptome research. CircRNAs can operate as microRNA sponges, influencing transcription as a result of their intricate engagement in normal transcriptional processes. Some early studies have showed that circRNAs play important roles in human disorders, including cancer. As the statistical association between PC and circRNAs grows, genetic and environmental studies are being built to investigate the possible targets of circRNAs in preventing carcinogenesis. Despite the fact that the association between circRNAs and PCs is well established, the integrated signaling pathways and molecular mechanisms of circRNA-modulated gene regulation are yet unknown. this research includes the latest development and research linking circRNAs to prostate cancer.

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INTRODUCTION

Since the history of genetics began in 1866 by Mendel, and until this moment in the present day, scientific discoveries continue to open new technical ways and mechanisms for understanding the work of human genes, and the impressive thing is that the more scientific discoveries in this field “molecular biology”, the greater the complexities and the mechanisms branched out more and more, these complexities and ramifications opened wide horizons for researchers in the field of biology until discoveries and conquests continued as if it were an endless line, and with every small extension towards the front, ramifications arise in addition to what was required of a review of previous theories or facts that turned out with the tremendous development of scientific techniques that they are wrong or at least need to be modified.

Although the DNA sequences in the human genome have been fully determined in 2003, it is still not fully understood, most genes have been identified through a combination of high-throughput experimental approaches and bioinformatics, but there is still much work to be done to learn the biological functions of the nucleic acid products. Despite the study of DNA and its components was and still is the dominant interest of most researchers and scholars as to the backbone of human genetic material, in the last decade interest has increased greatly in RNA as a special translator and technical engineer for DNA, so to speak.

RNA was formerly assumed to primarily act as a messenger, carrying DNA-encoded instructions to other molecules such as the ribosome, which might then use the information to produce proteins. The three most well-known RNA and main types involved in protein synthesis are messenger RNA (mRNA), transfer RNA (tRNA), and ribosomal RNA (rRNA) (Wang and Farhana, 2020)., all of which are found in all species. These and other forms of RNAs, like enzymes, primarily carry out biological activities. Some, on the other hand, have intricate regulatory biological functions. RNAs have crucial roles in both normal cellular processes and disorders due to their involvement in numerous regulatory mechanisms, their abundance, and their various activities. However, in the last 30 years, researchers have discovered that there are several forms of RNA **(Fig. 1).** These forms were previously dismissed as cellular junk. Noncoding RNA (ncRNA) the type that isn't involved in protein production is one of the most significant **(Slack and Chinnaiyan, 2019).**

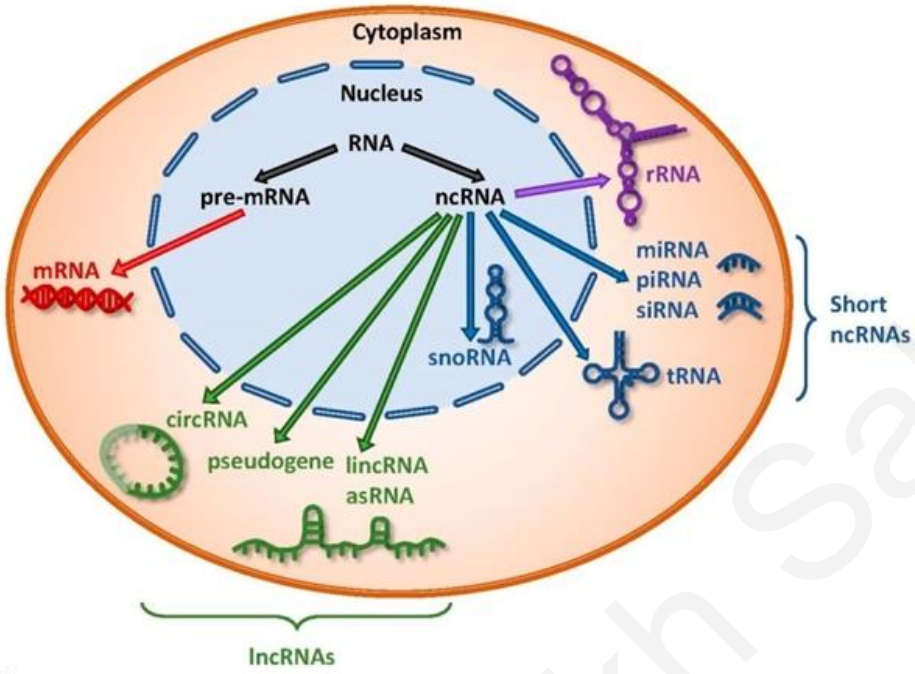


Figure 1. Coding and noncoding classes of RNA. Precursor messenger RNA (pre-mRNA) gives rise to protein-coding messenger RNA (mRNA). Noncoding RNAs (ncRNAs) include ribosomal RNA (rRNA) and other species that can be categorized into short and long ncRNAs. Short ncRNAs consist of microRNA (miRNA), Piwi-interacting RNA (piRNA), small interfering RNA (siRNA), transfer RNA (tRNA), and small nucleolar RNA (snoRNA). Long ncRNAs (lncRNAs) include long intergenic ncRNA (lincRNA), antisense RNA (asRNA), pseudogenes, and circular RNA (circRNA). **(Chan and Tay, 2018).**

Hundreds of ncRNAs have been discovered in recent years **(Fig.2),** and they are involved in a variety of processes including RNA maturation, transcription regulation, chromatin remodeling, and post-transcriptional RNA modifications, so ncRNAs play an important role in gene regulatory networks **(Panni et al., 2020).** The discovery of ncRNA species has transformed the field, changing how scientists think about physiology and disease progression **(Adams et al., 2017).** Although ncRNAs make up more than 90% of the RNAs produced by the human genome, the majority of the >50,000 known ncRNAs have only been identified in the last ten years and are mostly unstudied **(Esposito et al., 2019).**

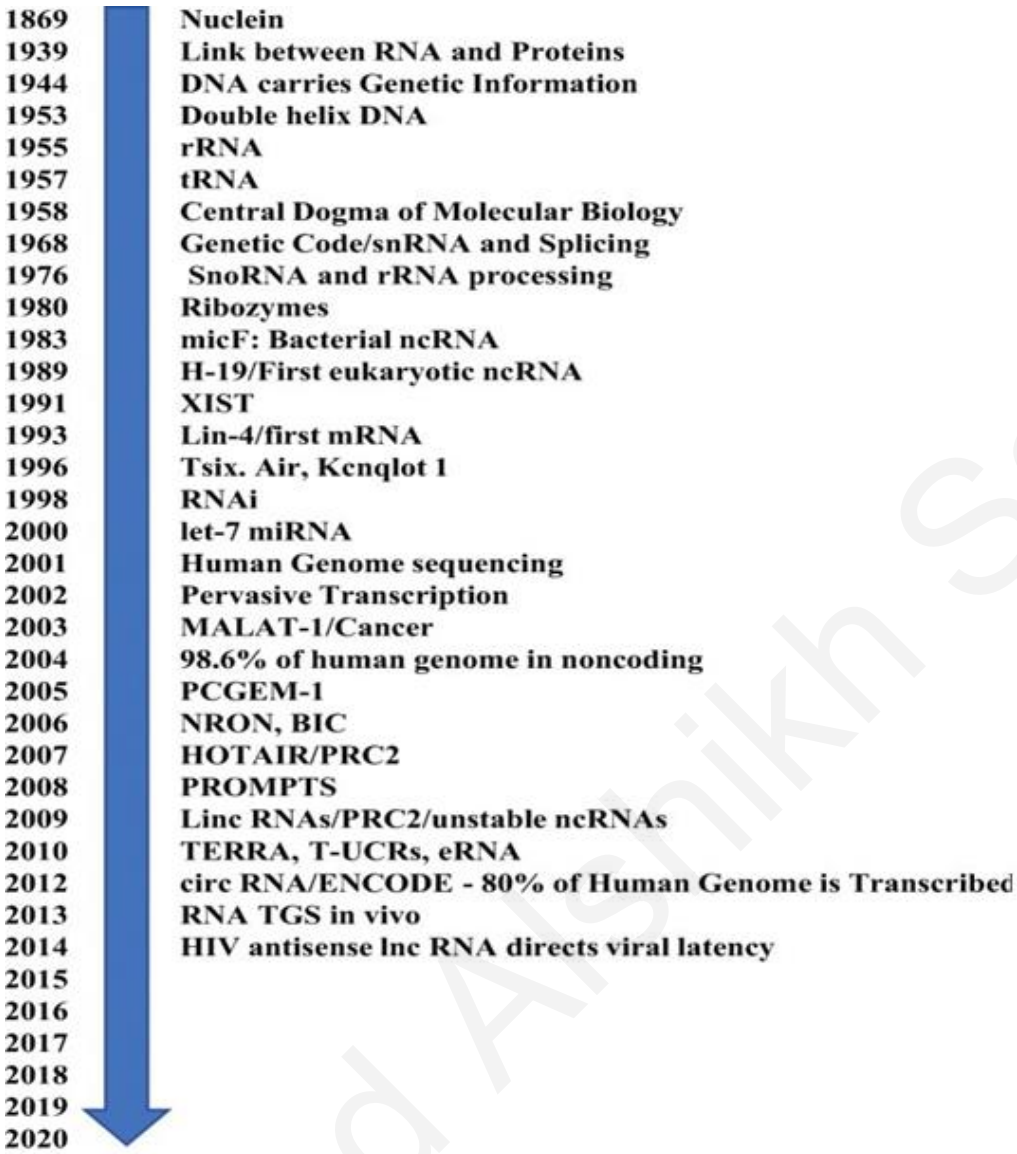


Figure 2: Timeline of molecular discoveries relating to noncoding RNA **(Bhatti et al., 2021).**

Many ncRNAs have now been discovered to have important roles in normal cellular function as well as illness, including cancer **(Romano et al., 2017).** Because certain tiny ncRNAs are sufficiently stable that they can survive in the bloodstream, they might be used to develop accurate and sensitive cancer screening tests **(Imaoka et al., 2016**). ncRNAs may be classified into several groups based on their size. microRNA (MiRNAs), tsRNAs, and piRNAs are examples of tiny ncRNAs that are significant in cancer. The lncRNAs, which are defined as untranslated RNAs longer than 200 nt and contain subclasses such as pseudogenes and circRNAs, are at the other

extreme of the size range **(Slack and Chinnaiyan, 2019**). The discovery of ncRNA has brought a new dimension to our knowledge of how cancer arises and how it might be treated.

It is now clear that noncoding RNA (ncRNA) plays a critical role in a variety of malignancies. Some of these ncRNAs are overexpressed in some malignancies, resulting in aberrant activation of CSC (Cancer Stem Cells) and dysregulation of various cell cycle signaling pathways. These ncRNAs are also known to be inhibited in several circumstances, preventing proper cell division. These are good candidates for cancer detection and therapy because of their important capacities and diversified functions **(Bhatti et al., 2021).**

Circular RNAs (circRNAs) have a nearly 30-year history **(Fig.3)**, they were discovered in RNA viruses in the 1970s, for the first time, and were once thought to be the result of transcriptional noise **(Chen et al., 2020).** CircRNAs are a kind of non-coding RNA (ncRNA) that is produced by back-splicing pre-mRNAs or long non-coding RNAs (lncRNAs) and are more stable than linear host genes **(Kristensen et al., 2019; Hanniford et al., 2020; Wang et al., 2021).** A rapidly rising number of circRNAs have been found in eukaryotic cells because of the developments in deep sequencing and analytics techniques, and circRNA expression patterns are tissue/development-specific **(Wu, Ji, and Zhao, 2020).**

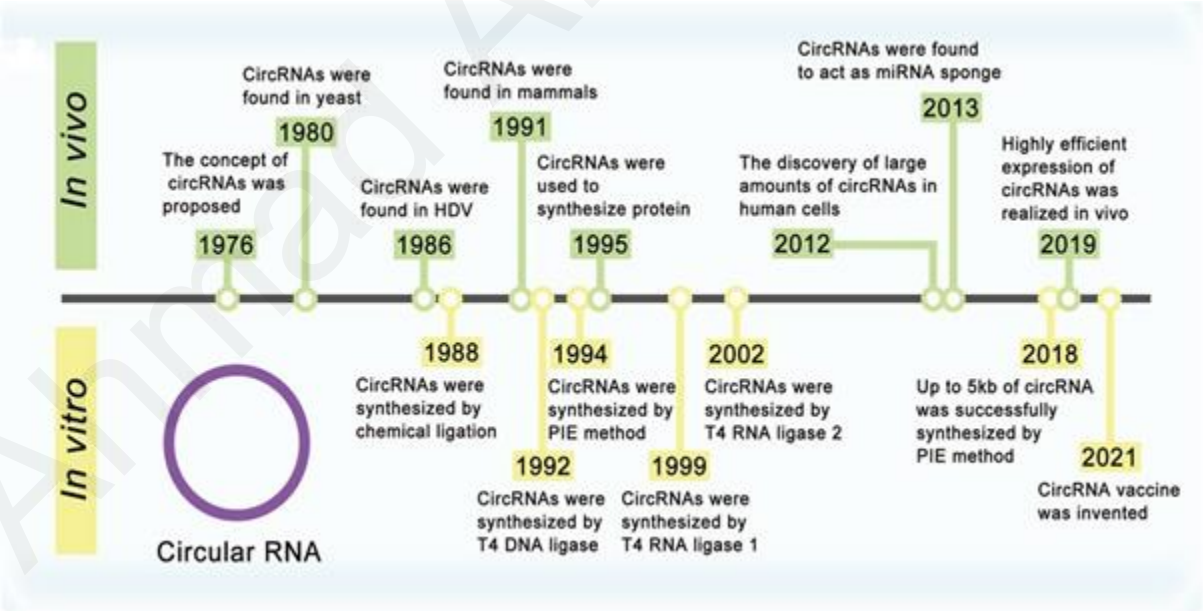


Figure 3: Timeline of circular RNA. **(Chen and lu,2021)**

CircRNAs had been generally overlooked in human cells, frequently dismissed as by-products of RNA splicing processes that produced mRNAs, but high-throughput RNA sequencing of libraries revealed that up to 20% of transcriptionally active genes expressed circRNAs **(Guo et al., 2014).** CircRNAs are characterized as exonic (ecircRNA), exon-intron (EIcircRNA), or intronic (ciRNA) based on their components **(He et al., 2021; Tao et al., 2021).** ecircRNAs are the most common circRNAs, and they are mostly created in vivo through a process known as back splicing **(Barrett et al., 2015).**

CircRNA is found in abundance in many cells and performs a variety of activities in them **(Fig. 4),** including functioning as a miRNA sponge, protein sponge, protein scaffold, and mRNA regulator. With the advancement of circRNA research, circRNA has become more relevant in medical applications, such as circRNA vaccines and gene therapy **(Chen and Lu, 2021).**

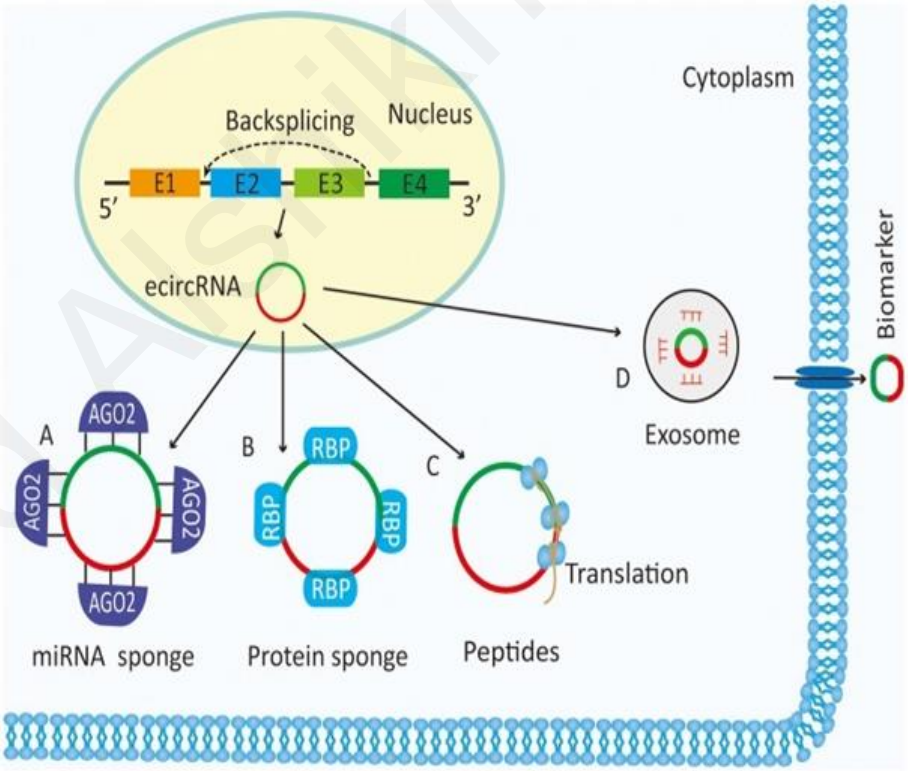


Figure 4: Functions of circRNAS. (A) circRNAs can act as miRNA sponges and subsequently regulate the expression of relevant target genes. (B) circRNAs can bind to several proteins and mediate their actions. (C) circRNAs can be translated into peptides or proteins. (D) circRNAs exist in the serum and other bodily fluids and can function as molecular biomarkers for the diagnosis and treatment of cancer. ecircRNA, exonic circRNA; circRNA, circular RNA; AGO2, Argonaute-2; RBP, RNA-binding protein **(Yang et al, 2021).**

circRNAs are mostly found in the cytoplasm and serve a variety of purposes. The microRNA (miRNA) sponge is the most well-known function of circRNAs **(Li et al., 2020; He et al., 2021).** Furthermore, they regulate the translation and stability of mRNA levels, as well as the activity of proteins **(Chen et al., 2020b; Huang et al., 2020).** Circ RNAs have a structural advantage that

makes them more stable, notably against exonuclease destruction, the enhancement of RNA stability has been a major problem in the creation of RNA vaccines. Fortunately, circRNAs have a lot of potential in this area **(Chen and Lu, 2021).** They vary from microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) in that they do not have a 5'cap and a 3'polyadenylated tail, and they can encode regulatory peptides **(Zhang et al., 2018).** Up to now, more than 15, 000 ecircRNAs have been discovered in people and mice, accounting for 15% and 40% of all circRNAs in humans and mice, respectively **(Dong et al., 2017).**

CircRNAs can interact with proteins, translated peptides, transcriptional and translational regulators, and compete with pre-mRNA splicing **(Xin et al., 2021).** CircRNAs have recently been shown to be linked with polysomes, and some of them include the start codon AUG and putative Open Reading Frames (ORF) of optimal length, indicating that circRNAs may have surprising protein-coding potential. Also, they can encode regulatory peptides, and there may be a secret proteome encoded by circRNAs **(Lei et al., 2020)**. Furthermore, in human cancer, circRNAs can affect host gene expression via a variety of regulatory mechanisms or indirect routes **(Wang et al., 2021).**

CircRNAs have been demonstrated to have an important role in tumor development in several studies, might be used as biomarkers to aid in the detection of some malignancies, and have been partially demonstrated to be molecular indicators of tumors in recent investigations **(Meng et al., 2017)**. miRNA response elements (MREs) are found in circRNAs and bind to miRNAs, preventing them from attaching to target mRNAs, circRNAs' ability to act as miRNA sponges is one of their most well-studied activities, several circRNAs regulate the expression of their host genes via miRNA sponges, serving as oncogenes in human cancers including proliferation, migration, invasion, metastasis, glycolysis, and apoptosis **(Chen et al., 2020).** Furthermore, circRNA-protein interactions have a role in target protein posttranslational regulation, such as ubiquitination and phosphorylation-mediated destruction **(Wang et al., 2021).** CircRNAs are suitable non-invasive diagnostic indicators for cancer detection because of these characteristics. Many circRNAs have also been shown to have biological roles in relevant cells, indicating that they might be used as therapeutic targets or tools **(Fang et al., 2020).**

Prostate cancer (PC) is a leading cause of death and disease in men. Each year 1.6 million men are diagnosed with the condition, and 366,000 men die from it **(Pernar et al., 2018).** According to the

Prostate Cancer UK Society, Prostate cancer affects one out of every eight males. You're at a considerably higher risk if you're over 50, black, or if your father or brother had it **(Prostate Cancer UK, 2018).** Adenocarcinomas account for almost all prostate cancers, these malignancies arise from gland cells, while some prostate cancers grow and spread rapidly, the majority do so slowly **(Cancer.org, 2018).** The most common cause of death from prostate cancer is metastasis, which happens when cancer cells migrate to other parts of the body **(Schatten, 2018).** Prostatectomy for primary prostate cancer and androgen deprivation for metastatic disease are the most common treatments, however, there are few alternatives for castrate-resistant prostate cancer **(Xia et al., 2018).**

The standard biomarker for prostate cancer diagnosis and management is serum prostate-specific antigen (PSA). However, because of its low specificity, the PSA test frequently leads to overdiagnosis and overtreatment **(Xia et al., 2018).** PSA testing, on the other hand, is restricted in its capacity to identify benign prostatic epithelial changes such as prostatitis or benign prostatic hyperplasia (BPH) from PCa **(Tan et al., 2019**). The prognosis of a given case of PCa is of great importance for the choice of patient treatment options, particularly regarding adjuvant treatment, and it is also an important indicator for judging the effects of treatment. The time from radical therapy to biochemical recurrence (BCR), the preoperative PSA value, the pathological stage, and the Gleason score (GS) are independent factors in the prognostic analyses of PCa **(Koo et al., 2018).** So, because the pathological stage and GS can only be identified by pathology, and GS alone cannot reliably advise prognosis, it's also crucial to uncover molecules that may accurately predict PCa prognosis using less traumatic ways before surgery **(Fischer et al., 2015).**

Liquid biopsy is the process of collecting and analyzing circulating components like circulating tumor cells (CTCs), cell-free DNA (cfDNA), and RNA (cfRNA) are being investigated as a possible source of PCa biomarkers **(Campos-Fernández et al., 2020).** Several initiatives are presently underway to develop early detection assays based on the detection of circulating RNA isolated from blood or urine in this context **(Cheung et al., 2019).** More and more circRNAs have been discovered to be inappropriately expressed and implicated in the incidence and progression of PCa, including cell proliferation, apoptosis, invasion, migration, metastasis, chemotherapy resistance, and radiation resistance, in recent years.

The majority of circRNAs influence cancer biology via a competitive endogenous RNA (ceRNA) regulation mechanism, however, some can also act via binding to proteins. Many clinicopathological aspects of PCa, including tumor grade, lymph node metastasis, and distant metastases, are linked to circRNAs. Furthermore, circRNAs have the potential to be used as diagnostic and prognostic biomarkers for PCa **(Liu et al., 2021).** Some circRNAs are tumor-specific, and their activities aren't always linked to parental genes, and they generally play a role in cancer growth on their own **(Vo et al., 2019).** About 19 % of the circRNAs discovered were tissue-specific and were assessed using bio-analysis criteria, Furthermore, several circRNAs have low expression abundance in PCa, even though the expression of their related progenitor genes does not alter much **(Vo et al., 2019).**

Cell survival (including cell cycle and apoptosis), migration, and invasion have all been studied as circRNAs play a part in the incidence and progression of PCa. CircRNAs' key strategy for regulating downstream targets is their role as miRNA sponges that control downstream gene expression, in all the studies on PCa, the majority of the circRNAs work in this manner. Many circRNAs that are involved in the growth of other malignancies are also involved in the development of PCa **(Ng, Mohd Mohidin, and Shukla, 2018).**

This work focuses on circRNA-related prostate cancer, it’s a way to present a brief, objective, and scientific presentation of circular RNA (circRNA) and its direct relationship with prostate cancer, explaining the mechanism of formation of circular RNA, it’s types and functions, and it’s effective and important role in cancers in general and prostate cancer in particular, explaining with a scientific view how the interference of circular RNA in the formation and development of prostate cancer on one hand, and it’s therapeutic and pharmacological possibilities on the other hand. Despite the difficulty of covering this topic in all its aspects considering the role of circular RNA in cancer is rather recent, that is, research and discoveries continue until this moment about this tiny molecule, which at an earlier stage was considered just biological noise, this view done to highlight the most important basic points in this subject, based on the most important and most recent studies related to this field.

OVERVIEW

Circular RNAs (circRNAs) are a remarkable kind of RNA molecule that was discovered over 40 years ago **(Fig.5).** By electron microscopy, circRNAs were found as circular RNA genomes in plant viroids in 1976 (Sanger et al., 1976). The first human circRNA was discovered in 1991 **(Nigro et al., 1991)**. By 2012, RNA-Seq has revealed genome-wide profiling of circRNAs, and it was discovered to behave as a miRNA sponge in 2013 **(Memczak et al., 2013).** The first commercial circRNA microarray was released in 2014, and the array was analyzed for its expression by Arraystar **(Qu et al., 2015)**. CircRNAs were proposed as cancer biomarkers in 2015, and they might be identified in exosomes **(Li et al., 2015).** CircRNAs were also discovered to have a long-life expectancy and high durability **(Enuka et al., 2015)**. In 2017, it was discovered that endogenous circRNA may be converted into functional polypeptides **(Yang et al., 2017)**. And a new technique for isolating very pure circRNA was established, which included RNase R treatment followed by polyadenylation and poly A+ RNA depletion (RPAD) **(Panda et al., 2017).**

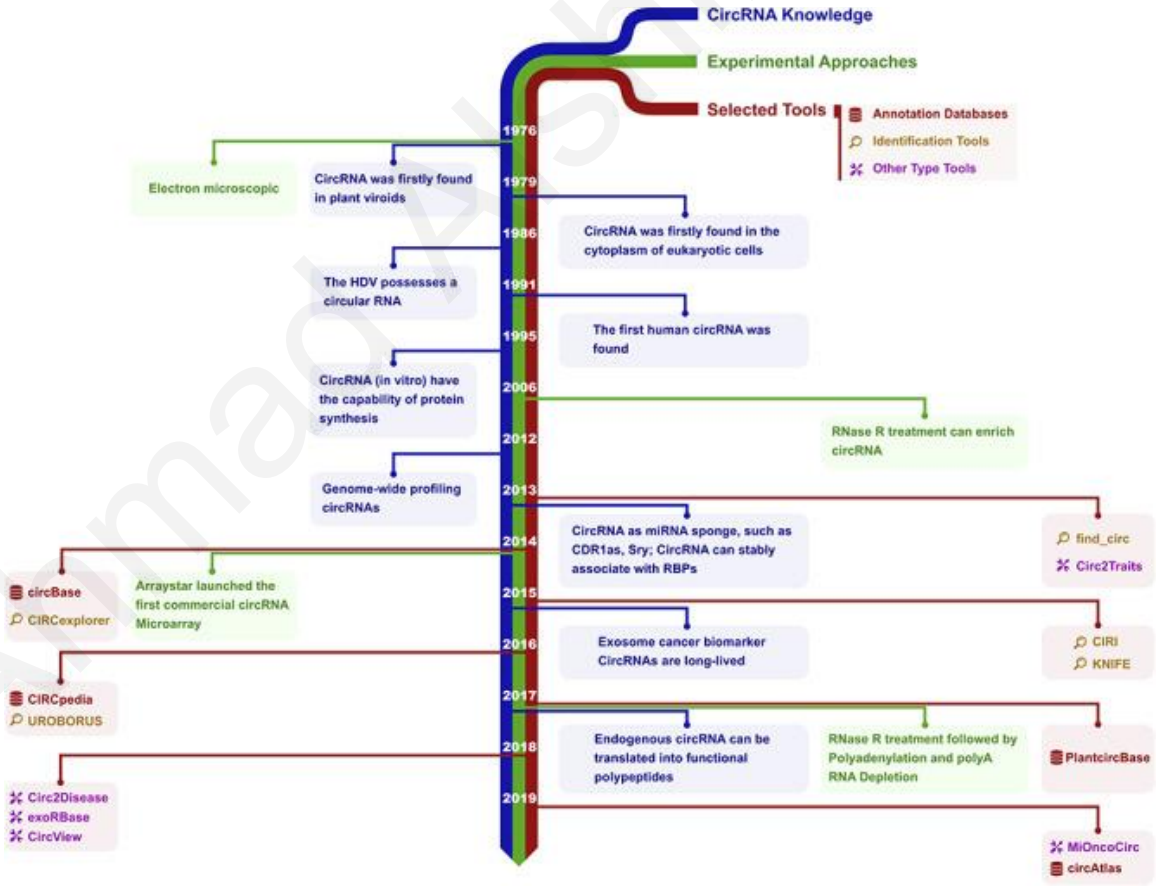


Figure 5: Historical timeline of circRNA research. The circRNA findings relating to biology, experimental techniques, and typical bioinformatics tools are marked in blue, green, and red, respectively **(Chen et al., 2020).**

Biogenesis of circRNA.

Circular RNAs (circRNAs) are a kind of single-stranded endogenous RNA with back-spliced covalently closed-loop structures. In general, circular RNAs have multi sub-classes including circRNAs from introns, which is circular molecules generated by spliceosomal splicing, tRNA splicing, and group I and II (self-splicing ribozymes) introns **(Nisar et al., 2021)**. Circular intronic RNAs (ciRNAs) are circularized intron lariats created by eukaryotic spliceosomal splicing in eukaryotes (ciRNAs). Viroids and the hepatitis delta virus (HDV), in this category single-stranded circRNAs are essential for RNA replication, in a process known as rolling circle RNA replication, circularity permits one initiation event to lead to numerous genomic copies. CircRNAs from intermediates in RNA processing reactions are made by splicing linear molecules from precursors and then circularizing them with a ligase, they are required for the rearrangement of RNA sequence order and for the synthesis of permuted tRNA genes in archaea. **(Circular RNAs: Biogenesis and Functions, 2018)**.

Noncoding circRNAs in archaea, here CircRNAs are formed from circularized tRNA introns that have been removed, Circularization of functional noncoding RNAs is expected to shield them against exonucleases while also promoting correct folding **(Jeck et al., 2012).**

Finally, the CircRNAs in eukaryotes are produced by back-splicing, back-splicing (a kind of exon scrambling) results in circular RNAs when a 5′ splice site is connected to an upstream 3′ splice site. In humans, more than 25,000 distinct circRNAs have been discovered (Nisar et al., 2021). Basically, circRNA is divided into three types based on the origin of their sequences: exonic circRNA (EcRNA), exon-intron circRNA (EIciRNA), and intronic circRNA (ciRNA) (Li et al., 2020). Most ecircRNAs are made up of back-spliced exons, in which the prim 3′ of the pre-mRNA splice donors are chemically attached to prim 5′ splice acceptors in reverse order **(Wilusz and Sharp, 2013).** These mechanisms mostly consist of three models **(Fig. 6)**.

In the first mode, a pre-mRNA is spliced, leading the upstream exon's 3′-hydroxyl to covalently link to the downstream exon's 5′-phosphate. Simultaneously, the sequence between the exons transforms into an RNA lariat with many exons and introns. The 2′-hydroxyl of the 5′-intron combines with the 5′-phosphate of the 3′-intron in the RNA lariat, followed by the 3′-hydroxyl of the 3′-exon interacting with the 5′-phosphate of the 5′-exon in the RNA lariat. An RNA double lariat and a circular RNA are formed as a result. Finally, the circular RNA's introns are deleted, yielding an ecircRNA or EIcirRNA.

The second mode was the direct back-splicing circularization. First, the upstream and downstream introns are paired, then the upstream intron's 2′-hydroxyl combines with the downstream intron's 5′-phosphate, followed by the 3′-hydroxyl of the 3′-exon interacting with the 5′-phosphate of the 5′-exon, as a result, a circular RNA is formed, and finally, the circular RNA's introns are deleted, yielding an ecircRNA or EIcirRNA.

The last mode is RNA-binding-protein-driven circularization. Initially, the upstream and downstream introns are bound by RNA binding proteins (RBPs). Next, the RBPs establish a bridge between the introns by being attracted to one other. Finally, the upstream intron's 2′-hydroxyl combines with the downstream intron's 5′-phosphate, followed by the 3′-hydroxyl of the 3′-exon interacting with the 5′-phosphate of the 5′-exon. As a result, circular RNA is formed. Finally, the circular RNA's introns are deleted, yielding an ecircRNA or EIcirRNA **(Wilusz and Sharp, 2013).**

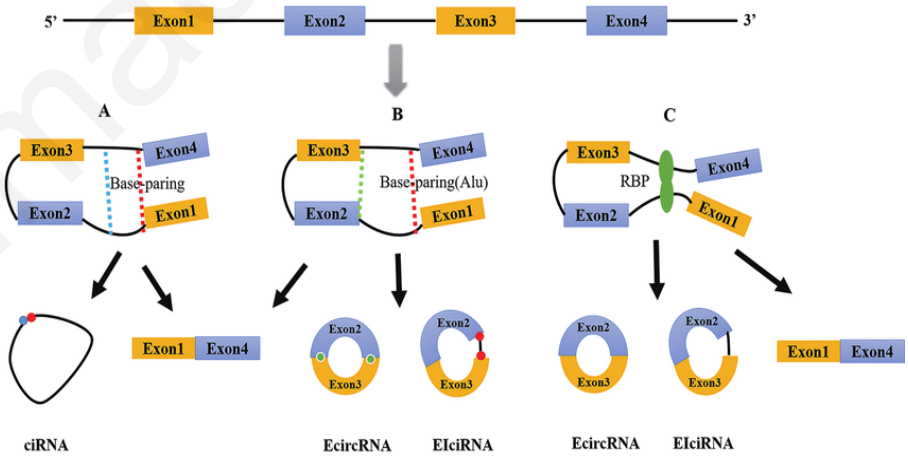


Figure 6: CircRNA biosynthesis models. (A) ciRNA formation by direct back-splicing: (B) ecircRNA and ElciRNA formation by direct back-splicing: (C) ecircRNA and ElciRNA formation by lariat-driven circularization. **(Yang et al., 2017).**

Circular intronic RNAs (ciRNAs), excised group I introns, excised group II introns, intron lariats, and excised tRNA introns are all circular RNAs that originate from introns **(Lasda and Parker, 2014).** The synthesis pathway of this type of circRNA is shown in **(Fig. 7).** Whereas the circular RNA from group I introns starts when the 5′-terminus of the intron is attacked as a nucleophile by exogenous guanosine(G), and the 5′-exon is cut off owing to transesterification. The 3′-hydroxyl of the free exon then acts as a nucleophile against the 5′-terminus of the 3′-exon, resulting in a linear intron. Then, a 2′-hydroxyl at the linear intron's 3′-terminus attacks a phosphodiester bond near the 5′-terminus, resulting in an RNA lariat circularized with 2′,5′-phosphodiester and releasing the 5′-terminal sequence, while the RNA lariat's 3′ tail is removed. While the circular RNA from group II introns takes place when the 3′-exon is released by the RNA precursor. This allows the 3′-terminus' 2′-hydroxyl attacks the intron's 5′-terminus, resulting in a circular RNA circularized with 2′,5′-phosphodiester. Lastly, RNA circular intron (ciRNA). A spliceosome first splices a pre-mRNA, resulting in an RNA lariat circularized with 2′,5′-phosphodiester, and the RNA lariat's 3′ tail is deleted **(Circular RNAs: Biogenesis and Functions, 2018).**

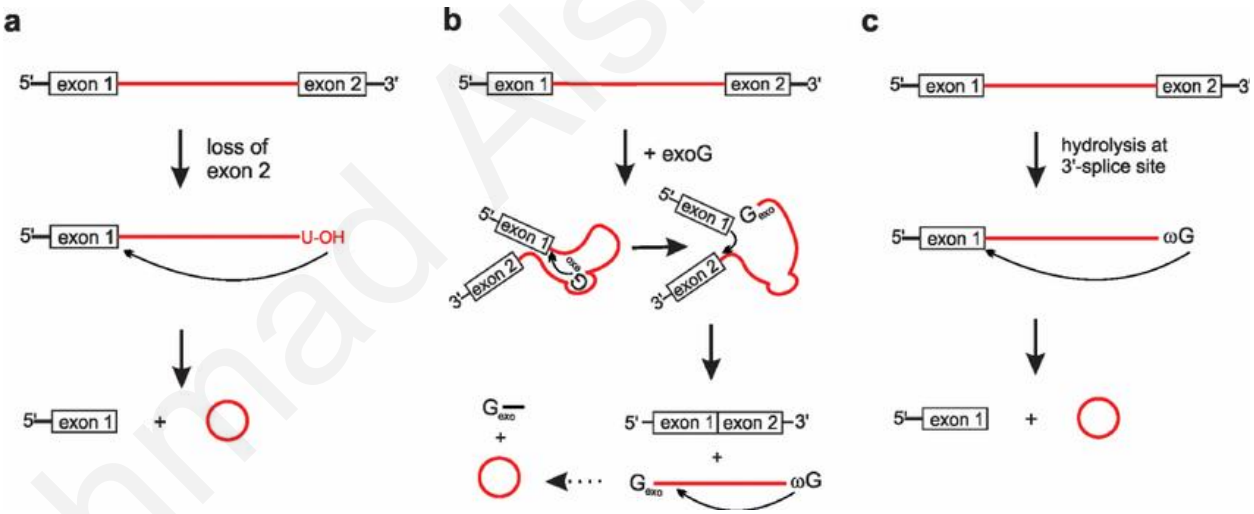


Figure 7: Intronic circRNAs formation. (a) Group II intron mediated circRNA formation. (b) Group I intron supported regular splicing. (c) circle formation by direct nucleophilic attack of G onto the 5-splice site. **(Petkovic and Müller, 2015).**

Exon-intron Circular RNAs (circRNAs) are circular RNAs that have both exons and introns circularized at the same time. Internal repeat sequences, which are comparable to ecircRNAs, may play an essential role in their development (Li et al., 2015). Yuan Gao et al. have discovered intergenic circRNAs using CIRI (CircRNA Identifier), a revolutionary circRNA detection technique that can detect circRNAs across the genome. It has two intronic circRNA segments bordered by GT-AC splicing signals that operate as the circular junction's splice donor and acceptor while producing an integrated circRNA **(Gao, Wang, and Zhao, 2015).**

Detecting and identification of circRNA.

For a variety of reasons, most circRNAs have remained unidentified until recently. Unlike miRNAs and other short RNAs, circRNAs are difficult to distinguish from other RNA species due to their size and electrophoretic mobility. Molecular approaches that rely on a polyadenylated free RNA end (such as rapid amplification of cDNA ends or poly(A) enrichment of samples for RNA-seq investigations) cannot detect circRNAs because they lack a free 3′ or 5′ end. Furthermore, a "backsplice" which is a critical property of circRNAs, is not unique to circRNAs, and early RNA-seq mapping methods filtered such sequences out. However, these issues have lately been resolved by the development of innovative bioinformatics tools such as exonuclease-based enrichment techniques, sequencing with longer reads and better throughput, and sequencing of ribosomal RNA (rRNA)-depleted RNA libraries **(Fig.8) (Jerk and Sharpless, 2014).**

Currently, available circRNA discovery approaches are all based on identifying back-spliced junction (BSJ) reads, and they are separated meanly into annotation-dependent such as MapSplice **(Wang et al., 2010)**, CIRCexplorer **(Zhang et al., 2014)**, and KNIFE **(Szabo et al., 2016)**. And de novo algorithms such as Find_circ **(Memczak et al., 2013)**, Segemehl **(Hoffmann et al., 2014)**, CIRI **(Gao, Wang, and Zhao, 2015)**, and CIRI2 **(Gao, Zhang, and Zhao, 2017)**. These approaches are employed not just for investigating circRNA loci directly, but also as the framework for more complex investigations. However, there is still an opportunity for improvement in present procedures.

It was noted that the prediction outputs of numerous detection algorithms were considerably unique from one another, and that they all had drawbacks in key areas of performance. Low sensitivity, low dependability, long duration, high RAM utilization, and/or a sophisticated pipeline were some of the drawbacks, which were caused by the intricacies of eukaryotic transcription and

splicing, as well as differential expression of circRNAs from diverse origins **(Hansen et al., 2015)**. On the other hand, microarrays can play a viable alternative to RNA-seq for circRNA identification since they require less bioinformatics knowledge **(Chen et al., 2018).**

Arraystar has released the first commercially accessible microarrays for human, mouse, and rat circRNAs until this current moment, which depends on this mechanism "Arraystar Circular RNA Arrays" **(www.arraystar.com, n.d.)**. Despite the wide range of applications and seq-libraries that assist in the detection and identification of circRNA, there are several challenges that arise at the interface. Technical artifacts in common RNA-seq techniques can lead to erroneous identification of circRNA isoforms. Technical artifacts can be introduced during the ligation and reverse transcription processes of RNA-seq library creation, as has been recognized for some time. Reverse transcriptase (RT) can cause significant template-switching abnormalities, in which two different RNA molecules are linked by RT, causing RNA-seq studies to fail when trying to find new RNA isoforms **(Yu et al., 2014)**. These artifacts can contribute to false positives in algorithmic prediction; thus, it is critical for algorithms that try to detect circular and linear RNA to assess and account for them.

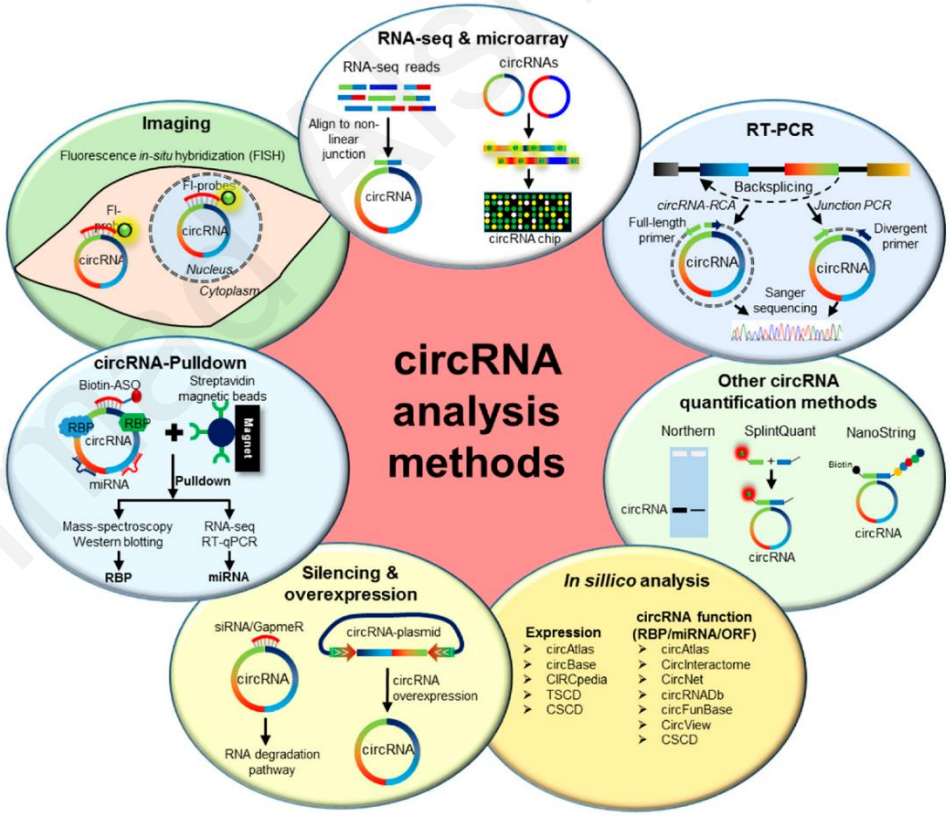


Figure 8: Different methods for circular RNA analysis. The genome-wide identification and quantification of circRNAs are done using RNA-seq and circRNA microarrays. RT- PCR of circRNA at the backsplice junction using divergent and full-length primers, followed by Sanger sequencing. verifies the expression of a particular circRNA. The quantification of circRNAS may be done using Northern blotting. SplintQuant, and NanoString. For in silico investigation of circRNA expression and function, several databases and web- tools have been produced. Loss-of-function study for circRNA may be done with siRNA/GapmeR for cireRNA silencing, while a gain-of-function analysis can be done with a plasmid vector overexpressing the circRNA of interest. CircRNA- associated cellular miRNAs and RNA-binding proteins (RBPS) may be studied utilizing antisense oligo-targeting circRNA junctions in circRNA pulldown experiments. Finally, fluorescent-tagged probes targeting the backsplice junction of the target circRNA can be used to observe circRNAs in cells **(Bejugam, Das, and Panda, 2020)**.

In addition, CircRNAs represent a minority of readings in most cell lines, about 1–3% of the total mRNA level **(Salzman et al., 2013)**. And although that some main tissue, such as platelets, have greater amounts of circRNA expression, most circRNAs are expressed at modest levels **(Szabo et al., 2016)**. Only reads aligned at the backsplice junction may be used to identify circRNAs in single-end RNA-seq data, since all other reads might have been produced by either a linear or circular isoform. Using junctional reads is challenging since reading density in any particular window might have large biases that are not yet understood, in addition to lowering sample size when compared to linear isoforms **(Lahens et al., 2014).** Furthermore, because exon boundaries include degenerate sequence motifs, a combination of homology and sequencing mistakes might result in false-positive alignments **(Gao, Wang, and Zhao, 2015).**

Systematic "blind spots" can result from biases in algorithms meant to reduce frequent sources of false positives, leading to inaccurate conclusions regarding the creation and control of circRNAs **(Szabo et al., 2016)**. Gene annotations or canonical U2 (major) splice signals are two common ways of reducing false positives **(Cheng, Metge, and Dieterich, 2015)**. Whereas U2 is a highly dynamic splicing component that is one of the most often mutated in malignancies **(Van der Feltz and Hoskins, 2019).**

RNase R, a highly processive 3′–5′ exonuclease that digests virtually all linear RNA with at least seven unstructured nucleotides at the 3′ end, is increasingly being used to enrich for circRNAs prior to sequencing **(Vincent and Deutscher, 2006)**, as another technique to exclusion the false-positive result. However, it is unlikely that enhanced enrichment procedures and sequencing technology would obviate the need for future algorithm improvement to improve specificity.

Furthermore, several known circRNAs are susceptible to RNase R in certain conditions **(Westholm et al., 2014).**

Nguyen et al. developed Circall which is a novel new approach for detecting circRNAs that is rapid and accurate, in this method, gene annotation is employed to create sequences of all BSJs of all probable exonic circRNAs, then used as a reference for reading alignment, based on an ultra-fast quasi-mapping algorithm, which makes it far faster than alternative procedures **(Nguyen et al., 2021)**. Therefore, to reduce the shortcomings of the current methods used in the detection and identification of circRNA, the scientific recommendations now to verify that BSJs are appropriately annotated, is to use two separate techniques or independent algorithms **(Hansen, 2018).**

Biological Function of circRNA.

CircRNAs were first assumed to be a result of splicing or "junk transcripts" because of their low quantity **(Liu et al., 2017).** Recent emerging investigations of circRNAs, on the other hand, have fundamentally transformed the perspective, suggesting that circRNAs not only have unique properties but also play important roles in physiological processes. **(Fig.9) (Aufiero et al., 2019).** Most circRNAs are exported from the nucleus to the cytoplasm shortly after their synthesis, except for intron-containing circRNAs **(Memczak et al., 2013).** The nucleus has been shown to have a large number of intronic circRNAs and EIciRNA **(Bentley, 2014).** This transportation is aided by spliceosome RNA helicase and ATP-dependent RNA helicase and is reliant on the length of circRNAs **(Rinaldi et al., 2016).** An online tool called CircInteractome (circRNA interactome) was recently created for mapping RNA-binding protein- and miRNA-binding sites on human circRNAs, which might be a useful initial step toward identifying and deep thought of the functions of any given circRNA **(Dudekula et al., 2015).**

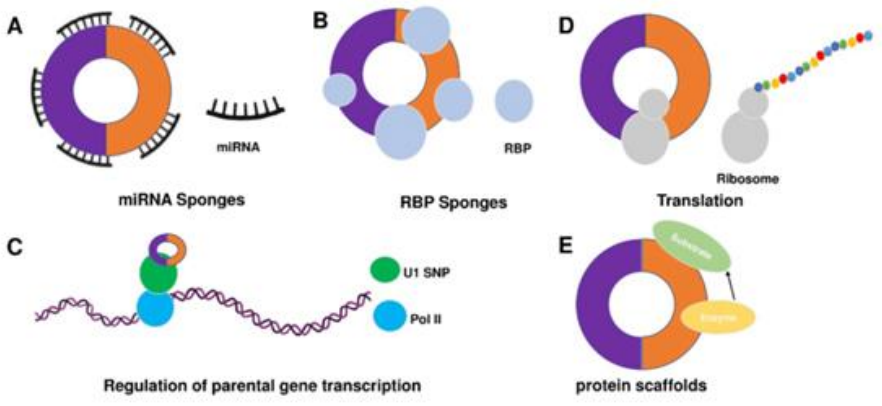


Figure 9: General functions of circRNA (A) circRNAs as miRNAs sponge, (B) circRNAs as RBP sponges, (C) circRNAs mediated regulation of the transcription of the genes, (D) circRNAs translated into proteins via some modification, (E) circRNAs act as dynamic scaffolding molecules that modulate protein-protein interactions **(Tang et al., 2021).**

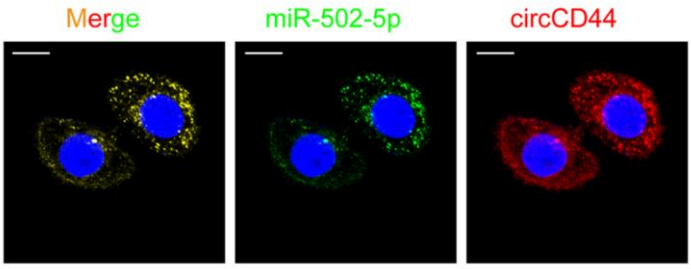
- ***CircRNAs function as miRNA sponges:***

One of the well-known roles of circRNAs is miRNA sponging, in which they can decrease miRNA function by attaching to target miRNAs directly or indirectly. For this functional consideration, the link between the circRNA interaction site and miRNA, as well as the mRNA target site, is critical **(Sharma et al., 2021).** As linear RNAs, circRNAs include miRNA response regions, permitting them to interact with miRNA for adherence to linear RNAs, implying a regulatory role in miRNA function and gene expression **(Taulli, Loretelli, and Pandolfi, 2013).**

Indeed, the discovery that circRNAs may be targeted by RNA interference suggested that the more durable circRNAs would compete with mRNAs for miRNA binding in the cytoplasm, therefore regulating gene expression **(Jeck et al., 2012)**. The best-studied circRNA to support this idea is ciRS7 (circular RNA sponge for miR7), which is made from the antisense transcript of the vertebrate cerebellar degeneration related 1 (CDR1). Over 60 conserved miR7 target sites are found in ciRS7, which is predominantly expressed in human and animal brains **(Hansen et al., 2013).**

By sponging distinct microRNAs, CircRNAs have been demonstrated to be implicated in a variety of pathogenic diseases. In triple-negative breast cancer, circCD44 has been shown to promote carcinogenesis by sponging miR-502-5p, where colocalization of circCD44 and miR-502–5p in the cytoplasm was detected in FISH experiments **(Fig.10) (Li et al., 2021).** In addition, sponging miR-145, overexpression of circLRP6 enhanced the progression of atherosclerosis **(Hall et al., 2019).** Hsa circ 0010729 has been proven to sponge miR-186 and upregulate HIF-1 to control endothelial cell regeneration. Circ CHFR interacts with miR-214-3p to enhance Vascular smooth muscle cell (VSMCs) proliferation, migration, and inflammation in response to oxidized low-density lipoprotein (oxLDL). CircRNAs may have a key role in CVDs through miRNA sponge effects, according to this research **(Dang, Liu, and Li, 2017; Lu et al., 2021).** Generally, the majority of circRNAs have been discovered to function as competitive endogenous RNAs

(ceRNAs) that influence miRNA activity by binding to miRNA response sites (MREs) **(Mitra, Pfeifer, and Park, 2018).**



Figur 10: FISH of circCD44 and miR-502–5p in the MDA-MB-231 cell line, scale bar: 20 μm. **(Li et al., 2021).**

- ***CircRNAs Interacts with Proteins:***

Another significant function of circRNAs is to function as protein decoys or antagonists. CircRNAs can interact with circRNA binding proteins directly (cRBPs) and control the translocation of specific proteins by binding to proteins **(Misir, Wu, and Yang, 2022)**. The mbl locus, which contains binding sites for the MBL protein, is the clearest experimentally validated evidence of a circRNA protein sponge **(Ashwal-Fluss et al., 2014)**. Other circRNAs, such circPABPN1, and circANRIL, interact with a target protein as well. In human cervical cancer HeLa cells93, circPABPN1 inhibits the translation of nuclear poly(A) binding protein 1 (PABPN1) mRNA by sequestering the RBP Hu- antigen R (HUR). As shown in a previous study where overexpressing of CircPABPN1 did not modify HuR levels but suppressed HuR binding to PABPN1 mRNA and as shown by Western blot analysis its reduced PABPN1 abundance **(Fig. 11) (Abdelmohsen et al., 2017)**. Numerous circRNAs have RBP binding sites which can be employed as scaffolds to help two or more proteins interact.

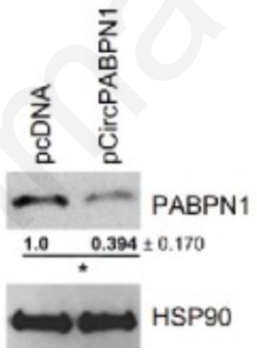


Figure 11: 48 h after transfecting HeLa cells with pcDNA3 or pCircPABPN1 the levels of PABPN1, HuR, and the loading control HSP90 were assessed by Western blot analysis. Following quantification of the bands on Western blots **(Abdelmohsen et al., 2017).**

Circ- Amotl1 **(Zeng et al., 2017)** and circ- Foxo3 **(Du et al., 2016)** serve as protein scaffolding that allows enzymes and their inputs to colocalize. circ- Amotl1 directly interacts with both 3-phosphoinositide-dependent protein kinase 1 (PDK1) and AKT1 (protein kinase B), facilitating

AKT1 phosphorylation by PDK1; AKT1 is then translocated to the nucleus, where it has been demonstrated to play a cardioprotective effect in an animal model **(Zeng et al., 2017).** Furthermore, circRNAs may direct particular proteins to specific cellular regions, as demonstrated by circRNA FECR1, which directs TET1 to the promoter region of FLI1, its host gene, resulting in a CpG site demethylation and active transcription **(Chen et al., 2018).**

- ***CircRNAs as protein translators:***

The majority of circRNAs are found in the cytoplasm, where they serve as miRNA or protein decoys, transporters, or scaffolds. Some circRNAs, on the other hand, are kept in the nucleus, where they may obstruct transcription or encourage alternative splicing **(Kristensen et al., 2017).** ElciRNAs have been demonstrated to bind with U1 snRNP and connect with RNA pol II, promoting the transcription of their parental genes **(Li et al., 2015).** CircRNAs have been shown to serve as translation templates and may encode proteins or peptides important in tumor etiology and progression **(Zheng et al., 2019).** Furthermore, circ-ZNF609 was shown to be linked with the ribosome and capable of being translated into a protein, hence influencing myoblast proliferation **(Legnini et al., 2017)**. Yang et al. have found that N-methyladensine (m6A) can accelerate the beginning of protein translation from circRNAs in human cells **(Yang et al., 2017).** YTHDF3, an m6A recognition protein, connects to the circRNA modification site and activates eIF4G2 and other translation initiation factors to induce circRNA translation **(Zhang et al., 2018).**

- ***CircRNAs as gene transcriptional regulator:***

Although circRNAs lack effective translation initiation structures, unlike many linear mRNAs with a 5' cap and a 3' poly-A tail but can be translated after an internal ribosome entry site (IRES) is established **(Wesselhoeft, Kowalski and Anderson, 2018)**. Chen et al. discovered that after introducing an IRES into a synthetic circRNA, eukaryotic ribosomes may commence translation, indicating that the 5' end of mRNA is not always the entrance point for the ribosomal 40S subunit **(Chen and Sarnow, 1995)**. In addition to that, by interacting with the elongation Pol II complex, inhibition of ci-ankrd52 and ci-sirt7 cause a considerable decrease in the transcription of their parental genes **(Zhang et al., 2013).** According to Liu et al. ElciRNAs, such as circEIF3J and circPAIP2 may bind with U1 small nuclear ribonucleic proteins (snRNPs) through RNA-RNA interaction when localized in the nucleus **(Lu and Xu, 2016)**. Then, at the promoters of parental genes, the elciRNA-U1 snRNP complexes may interact with the Pol II transcription complex to

boost gene expression **(Li et al., 2015).** Circ2082 binds to RMB3 and informs Dicer where to go in the cell. Dicer's cytosolic localization was restored after knocking down circ2082 **(Fig.12) (Bronisz et al., 2020).** Recently, Stoll et al. have demonstrated that the intronic circle ci-Ins2, which is found mostly in the nuclei of pancreatic cells, can control insulin production by interacting with the TAR DNA-binding protein (TDP-43) **(Stoll et al., 2020).**

- ***Other biological functions of circRNAs:***

CircRNAs have been linked to several cancer-related symptoms thus far. CircRNAs generated from the tumor suppressor gene Foxo3 have been discovered to enhance cancer cell apoptosis in a variety of ways **(Du et al., 2016).** circFoxo3 has been linked to angiogenesis and cell cycle progression inhibition **(Yang et al., 2015).** CircZNF292, like circFoxo3, has been found to have tumor-suppressor characteristics by inhibiting cell cycle progression **(Yang et al., 2016).** Another circRNA that promotes angiogenesis via the vascular endothelial growth factor A (VEGFA)/VEGFR2 signaling pathway is circMYLK **(Zhong et al., 2022).**

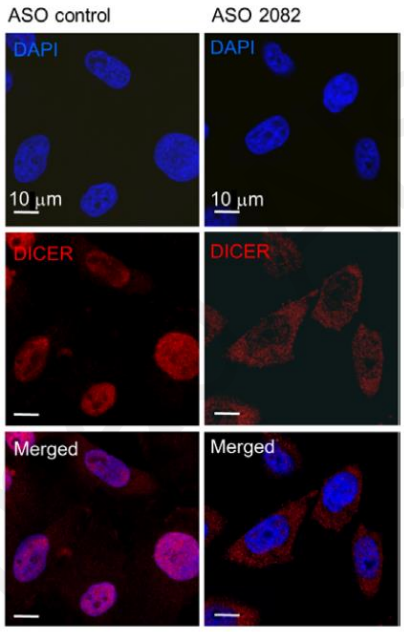


Figure 12: Representative images of cultured GSC (n = 3) transfected with ASO control or circ2082. DAPI staining (blue) and DICER immunohistochemistry staining (red) analysis were performed. **(Bronisz et al., 2020).**

Xuan et al. looked at the expression of circRNA in a group of tissues from laryngeal squamous cell carcinoma (LSCC). They discovered that two circRNAs, hsa circRNA 100855 and hsa circRNA 104912, were up- and down-regulated in cancer tissues, respect, as compared to non-neoplastic tissues **(Xuan et al., 2016)**. Higher hsa - circRNA 100855 expression and lower hsa - circRNA 104912 expression were seen in patients with T3-4 stage, neck nodal metastases, or

advanced clinical stage **(Guo et al., 2019).** Numerous additional circRNAs are likely implicated in cancer's hallmarks **(Fig.13)** since many studies have revealed an influence of circRNA knockdown or amplification on cancer cell proliferation rates in culture without investigating the molecular processes.

Figure 13: Circular RNAs involved in the hallmarks of cancer **(Kristensen et al., 2017).**

The Role of CircRNAs in Prostate Cancer.

CircRNA research has been conducted in most solid cancers. The majority, on the other hand, was meant to look at one or more predetermined circRNAs with little chance of discovering new circRNA species. CircRNA expression is commonly compared between cancer tissues and neighboring noncancerous tissues in most research, and this is generally followed by subsequent functional investigations. Most of the research used microarray analysis, followed by RT-qPCR confirmation of identified circRNAs in larger cohorts **(Kristensen et al., 2017).**

Prostate cancer (PCs) is one of the most frequent cancers in men across the world. Circular RNAs (circRNAs) have been implicated in the development and progression of several malignancies, and they have significant promise as new biomarkers, according to mounting data **(Wu et al., 2020).** The number of circRNAs identified in PC is rising as innovative technology is discovered. Furthermore, it is well accepted that androgen deprivation therapy is the most common treatment on PC therapeutic measures, with the impact of transition from androgen-dependent to androgen-independent being incredibly significant. However, as the statistical association between PC and circRNAs grows, genetic and epigenetic studies are being developed to investigate the possible targets of circRNAs in preventing carcinogenesis **(Fig.14).**

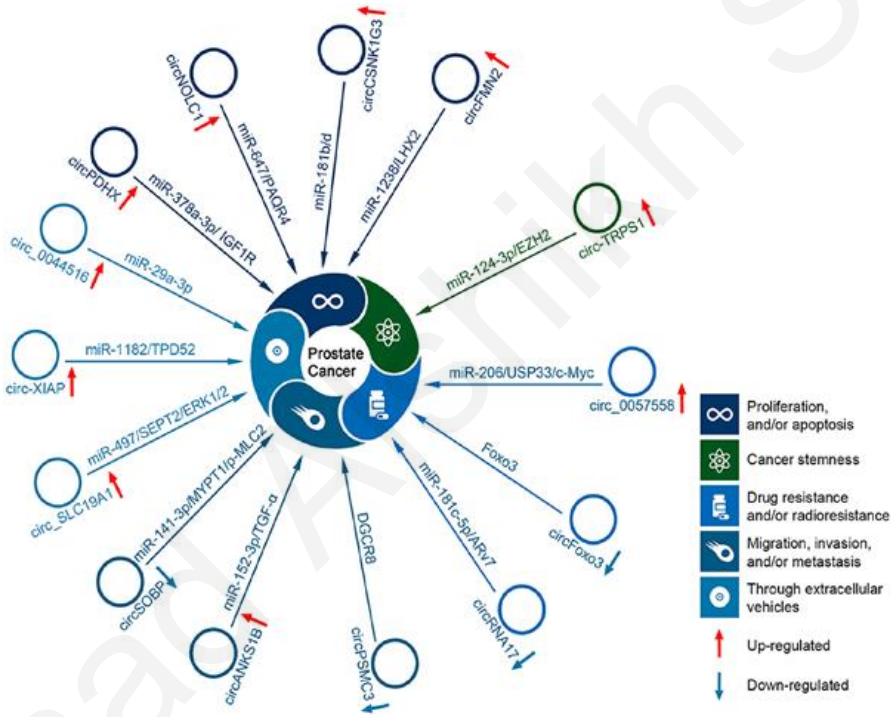


Figure 14: Schematic diagram for the typical functioning of circRNAs in PCs **(Chao et al., 2021).**

Even though the association between circRNAs and PC is well established, the integrated signaling pathways and molecular mechanisms of circRNA-modulated gene regulation are yet unknown. By functioning as miRNA sponges, circRNAs primarily serve regulatory functions in the pathogenic development of PCs. CircRNAs in PCs can potentially bind to proteins and have regulatory

functions, according to certain research. It is worth noting that while circRNAs can be translated into polypeptides, no evidence of this process has been identified in PCs research.

According to the competing endogenous RNA (ceRNA) hypothesis, circRNAs can interact with mRNA for attaching to miRNAs, favorably influencing miRNA target genes (Hansen et al., 2013). circRNAs interacting with miRNAs, on the other hand, have been shown to boost miRNA suppression on downstream target genes in a few studies. Wu et al., for example, discovered that circRNA17 suppresses ARv7 expression via sponging to miR-181c-5 **(Wu et al., 2019).** Similarly, circHIPK3 in PCs functions as a molecular sponge for miR-193a-3P. circHIPK3 upregulates MCL1 expression in PCs via targeting miR-193A-3P's 30 UTR, which normally suppresses it **(Chen et al., 2019).**

Zheng et al. proved that the interaction of circ KATNAL1 with miR-145-3p has been shown to suppress the expression of the downstream target gene WISP1 **(Zheng et al., 2020).** By interacting with RBPs, circRNAs play a critical function in gene expression regulation at the transcriptional level. The RNA-binding protein FUS interacts with circ0005276 to enhance XIAP expression, which promotes the onset and progression of PCs **(Feng et al., 2019).**

In another publication, circAGO2 binds to HuR and suppresses AGO2/miRNA-mediated downregulation, boosting carcinogenesis and metastatic spread in PCs **(Chen et al., 2019).** Through bioinformatics analysis, Wu et al. found that hsa-circ 0024353–hsa-miR-940–PDE7B, hsa circ 0024353–hsa-miR-1253–DMRT2, and hsa circ 0085494–hsa-miR-330-3p–TGFBR3 are three circRNA–miRNA–mRNA interaction axes that may give unique insights into the putative processes behind PC's formation **(Wu et al., 2020).**

On other hand, Overexpression of circSOBP which is a novel circular RNA detected by Chao et al. inhibited PCs migration, invasion, and metastasis in vitro and in vivo, and CircSOBP bound miR-141-3p and controlled the MYPT1/p-MLC2 axis in a mechanism. Furthermore, MYPT1 knockdown abolished the inhibitory impact of circ-SOBP on PCs cell migration and invasion **(Chao et al., 2021)**. Hsa circ 0030586 is another circRNA overexpressed in PCs cells and may function as a sponge for miR-145-3p, promoting EMT via PI3K-AKT signaling **(Luo et al., 2021).**

Yan et al. used RNA-seq to identify EMT-related circRNAs in IFN-g-induced EMT cells and discovered that has-circ-0001165 and has-circ-0001085 were EMT-related circRNAs, whereas the

epithelial-mesenchymal transition (EMT) is implicated in the spread of malignant tumors, and CircRNAs have a role in this process **(Yan et al., 2020).** Furthermore, in PCs tissues, Han et al. discovered a decrease in circSMAD2. Through suppression of miR-9, recovery of circSMAD2 might reduce the defective EMT process **(Han et al., 2019).** According to Li et al., circ-0016068 induced PCs cell EMT through modulating the miR-330-3p/BMI-1 axis **(Li et al., 2020).**

The importance of targeting prostate-specific circRNA and finding novel therapeutic targets cannot be overstated. Although several studies have described the biological effects of circRNAs in prostate cancer, due to a lack of experimental verification, it is unclear whether ones are prostate-specific. It seems that the discovery of prostate-specific circRNAs will be the focal point of future studies.

- ***CircRNA as Diagnostic and Prognostic Biomarkers:***

PSA has been the standard biomarker for screening, diagnosing, and monitoring PCs since its debut in 1987 as a serum tumor marker **(Kellokumpu-Lehtinen et al., 1989).** The use of PSA, on the other hand, was deemed to have a minor advantage in terms of lowering PCs morbidity, but with problems such as diagnostic errors and overtreatment. Furthermore, many variables such as trauma, inflammation, and age may influence PSA levels **(Hu et al., 2015)**. The gold standard approach for confirming the existence of cancer in the prostate is a prostate biopsy, although this procedure is invasive and has significant risks, such as infection and bleeding **(Borghesi et al., 2017).** CircRNAs have a lot of promise as PCs biomarkers for diagnosis and prognosis.

To begin with, circRNAs are highly conserved and extensively expressed in a range of organs as distinct endogenous non-coding RNAs. Second, circRNA possesses a covalent closed-loop structure and is resistant to destruction by RNA exonucleases. Finally, PC-related circRNAs have been found in human body fluids such as blood and urine, in addition to physical tissue **(Kolling et al., 2019; Memczak et al., 2015).** Because of their universal expression patterns and unique properties such as tissue selectivity, stability, and evolutionary conservation, circRNAs might be a suitable biomarker **(Xia et al., 2016).** Salzman et al. discovered that circRNAs not only make up a significant portion of cellular RNA but that they are also expressed differently in different cell types **(Salzman et al., 2013).** The observations of circRNA dysregulation across different forms of cancer support this. The presence of circRNA in human physiological fluids such as saliva,

blood, and stomach juice add to the evidence that it might be used as a disease biomarker **(Bahn et al., 2015).**

In prostate cancer, a variety of RNA biomarkers have been studied, however, there is a paucity of research explaining the role of circRNA as a biomarker. Kong et al. discovered that circSRAMRCA5 (hsa circ 0001445) is up-regulated in four prostate cancer cell lines (LNCAP, 22RV1, DU145, and PC-3) when compared to a normal prostate cell line (WPMY-1) and in 21 prostate cancer tissue samples when compared to comparable normal prostate tissue samples **(Kong et al., 2017).** This study also discovered that androgens could impact circSMARCA5 expression, as circSMARCA5 levels rose in a dose-dependent way in response to dihydrotestosterone (DHT) levels **(Kong et al., 2017).**

In comparison to normal prostate cell lines (LNCAP, DU145, PC-3, and PC-3MIE8), Dai et al. discovered that circRNA-MYLK (has_circ 0141940) is up-regulated in prostate cancer cell lines (LNCAP, DU145, PC-3, and PC-3MIE8) (WPMY-1). In comparison to comparable normal prostate tissues, the researchers discovered that circRNA-MYLK is upregulated in 17 prostate cancer tissues, the researchers also discovered that up-regulation of circRNA-MYLK served as a miRNA sponge, lowering miR29a levels **(Dai et al., 2018).** Xia et al investigated the link between circ_0062019, circ_ 0075538 expressions, and aggressive cancer. They used a Receiver Operating Characteristic (ROC) curve to assess the diagnostic effectiveness of differential circRNAs in differentiating between prostate cancer and Benign prostatic hyperplasia (BPH) tissues **(Fig.15),** indicating that the two circRNAs may be linked to prostate cancer progression. Circ_0057558 was also found to be strongly connected with total cholesterol, suggesting that it may be linked to lipid metabolism in prostate cancer patients **(Xia et al., 2018)**.

As had been proven that membrane fluidity, cell development, and resistance to chemotherapeutic drugs can all be affected by changes in lipid content, and PCs are hormone-dependent cancer in which cancer cells primarily rely on lipid oxidation for development **(Deep and Schlaepfer, 2016).**

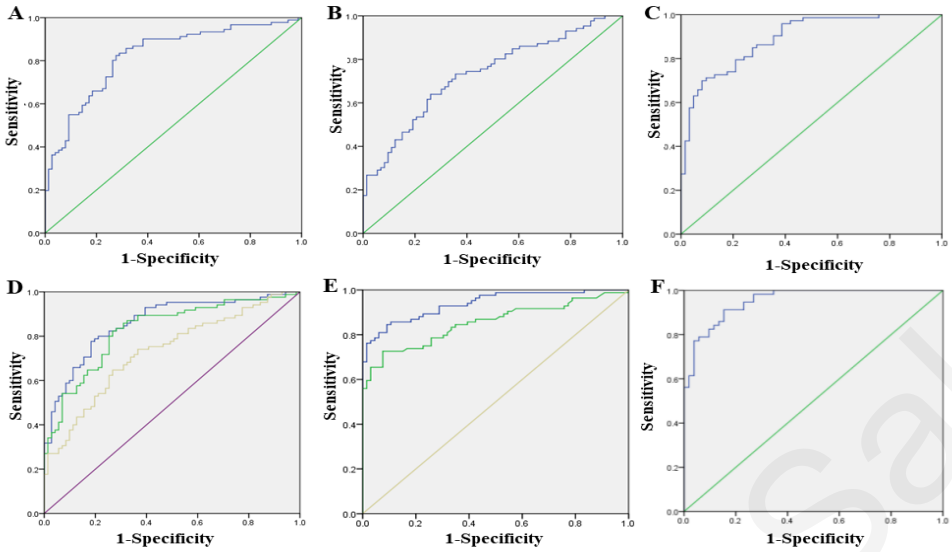


Figure 15: The expression levels of differential circRNAs are shown by a ROC curve. circ 0062019 and circ 0057558: (A, B) and the host gene SLC19A1 (C) in PCs patients and BPH controls; the 2 circRNAs combination (D), the 2 circRNAs and PSA combination (E), the 2 circRNAs, PSA, and SLC19A1 combination (F); the 2 circRNAs, PSA, and SLC19A1 combination (G); the 2 circRNAs, PSA (F). Univariate (log-rank) analysis was used to examine the ROC curves **(Xia et al., 2018).**

ROC curves were used to evaluate the diagnostic efficacy of differential circRNAs in differentiating between prostate cancer and BPH samples. The area under the curve (AUC) of circ 0062019, circ 0057558 and SLC19A1 were 0.828, 0.729 and 0.891, respectively (Fig. 12A-C). But even though PSA is the main clinical marker for early diagnostic testing of prostate cancer, the AUC of two differential circRNAs combined seems to be much better (0.861, Fig. 12D) than PSA alone (which AUC of serum PSA was 0.854), demonstrating that different levels of these two circRNAs could help distinguish PCs patients from non-PCs patients and combing them could improve diagnostic efficiency. They looked at the PSA level in conjunction with the results of the two distinct circRNAs. The AUC was 0.938, the sensitivity was 84.5 percent, and the specificity was 90.9 percent, according to the findings (Fig. 12E). The AUC increased to 0.952 when the circRNAs, PSA, and SLC19A1 were combined (Fig. 12F) **(Xia et al., 2018)**.

In addition, as shown in **(Fig.16)** Song et al. identify three circRNAs, including has_ circ_0001633, has_circ_0001206, and has_circ_0009061, from five pairs of PCs and paraneoplastic tissue samples, with AUCs of 0.809, 0.774, and 0.711, respectively **(Song et al., 2019).**

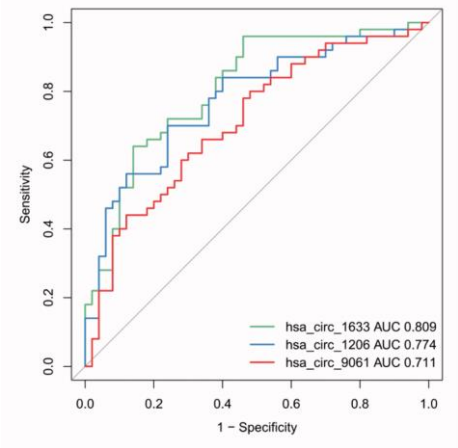


Figure 16: ROC curves for hsa_circ_0001633, hsa_circ_0001206, and hsa_circ_0009061. **(Song et al., 2019)**

Furthermore, exosome-derived circ 0044516 is expressed in PCs tissues and patients' blood **(Li et al., 2020)**, and circZMIZ1 expression in PCs patients' plasma is greater than that in matched BPH patients' plasma (Jiang et al., 2020), suggesting that both are potential diagnostic indicators. In PCs cell lines and tissues, circITCH expression is dramatically decreased, and the low level of circITCH expression is strongly linked to preoperative PSA levels, in specimens from 342 patients having radical prostatectomy, circITCH had an excellent AUC of 0.812 (95 percent CI: 0.780–0.845) for discriminating tumor tissues from surrounding tissues **(Huang, Chen, and Yuan, 2019).**

A technique of diagnosis that combines circRNAs and linear transcription studies is also available. To verify this, the ArrayStar microarray was used to select six circRNAs whose host genes play important roles in PCs and two circRNAs previously reported in previous studies from six pairs of PCs tissue and matched normal samples for diagnostic efficiency analysis to distinguish adjacent normal (n = 79) and malignant (n = 115) tissue samples from PCs specimens. The AUC of circATXN10 coupled with linSTIL was 0.892, which was higher than the AUCs of circRNA and linear transcription alone **(Fig17) (Rochow et al., 2020).**

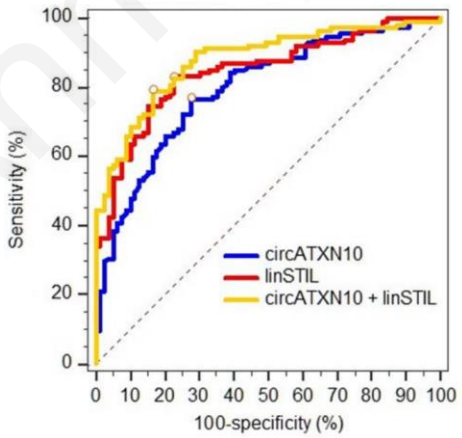


Figure 17: ROC curve and decision curve analyses of circATXN10 and linSTIL as individual markers and in combination for discrimination between adjacent normal and malignant tissue samples **(Rochow et al., 2020).**

ROC curve and other approaches investigations by Hansen et al. revealed that four circRNAs (circABCC4, circFAT3, circATRNL1, and circITGA7) had AUCs over 0.7, indicating that they might be used to diagnose PC **(Hansen et al., 2022).** They also created and validated a unique 5-circRNA prognosis signature for PC (circKMD1A, circTULP4, circZNF532, circSUMF1, and circMKLN1), which is the first report of a prognostic circRNA signature for PC that has considerable independent predictive value in different PC patient populations. This 5-circRNA signal, according to Hansen et al., might possibly help in the identification of individuals who would benefit from more intensive treatment, such as radiation and androgen restriction therapy (ADT) **(Hansen et al., 2022).** Indeed, to determine if circRNAs can be used as biomarkers in the clinic, a substantial number of clinical samples, such as plasma and urine, will be required for practicability testing, and that is what represents a major disadvantage facing this kind of study due to the small amount of circRNA contained in biological samples.

- ***CircRNAs as a regulator for PCs progression:***

Although circRNAs play critical roles in cancer formation, their activities in prostate cancer have yet to be extensively explored **(Huang et al., 2019).** However, studies and research are continuing until this moment, revealing the important role that circRNA plays in PCs. The phosphatidylinositol 3-kinase (PI3K)/Akt pathway is typically active in PCs, and it promotes tumorigenesis, propagation, and invasion **(Blattner et al., 2017).** The phosphatidylinositol kinase-related kinase mammalian target of rapamycin (mTOR) kinase plays an important role in PI3K/Akt pathway activation by constructing mTOR-complex 1 (mTORC1) and mTOR-complex 2 (mTORC2) in PCs **(Zoncu, Efeyan and Sabatini, 2010).**

In the work of Shi et al., they revealed that the circRNA circMBOAT2 (has_circ_0007334) was overexpressed in human PCs tissues, and that overexpression of has_circ_0007334 was linked to a poor prognosis in PCs patients. Has_circ_0007334 increased PCs proliferation and metastasis by sponging miR-1271-5p, which upregulated mTOR expression and activated the PI3K/Akt signaling pathway further **(Shi et al., 2020).** Furthermore, the fundamental component of the microRNA (miRNA)-induced silencing complex, Argonaute 2 (AGO2), plays an important role in carcinogenesis and aggressiveness including PCs **(YOO et al., 2010).**

Chen et al. identify circAGO2, a new regulator of AGO2-miRNA interactions and tumorigenesis, as an intronic circular RNA (circRNA) produced from the AGO2 gene. CircAGO2 stimulates the proliferation, invasion, and metastasis of cancer cells in vitro and in vivo, and it is upregulated in prostate cancer. CircAGO2 physically interacts with the human antigen R (HuR) protein to facilitate its activation and enrichment on the 3'-untranslated region of target genes, resulting in reduced AGO2 binding and repression of AGO2/miRNA-mediated gene silencing linked to cancer progression **(Chen et al., 2019).** However, the link between circABCC4 and cancer in humans is mostly unclear.

The biological activities of circABCC4 in prostate cancer progression were examined by Huang et al., and the fundamental process was shown. They discovered that circABCC4 was significantly up-regulated in prostate cancer tissues and cell lines, and that sponging miR-1182 in prostate cancer cells enhanced FOXP4 expression. CircABCC4 knockdown, on the other hand, significantly reduced prostate cancer cell proliferation, cell-cycle progression, migration, and invasion in vitro. In addition, silencing the circRNA inhibited tumor development in vivo **(Huang et al., 2019).** These findings suggest that circABCC4 promotes FOXP4 expression by sponging of miR-1182, which aids the malignant behavior of prostate cancer. **(Fig.18)**

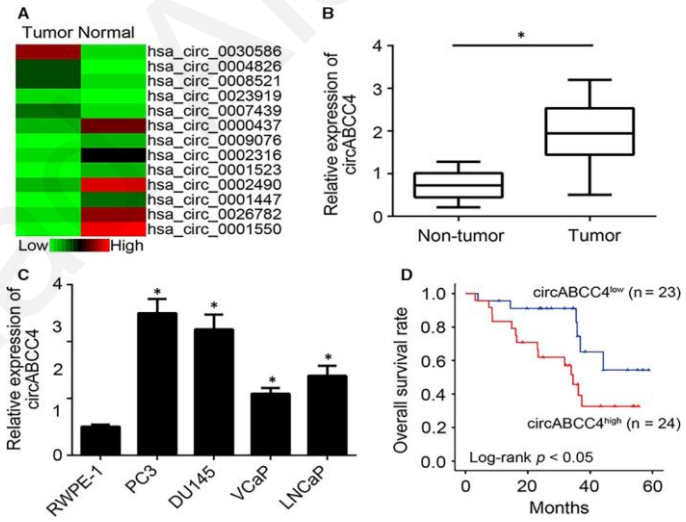


Figure 18: Eexpression of circABCC4 in prostate cancer tissues. (A) according to a microarray dataset, heatmap of differentially expressed circRNAs in pairs of prostate cancer and neighbouring normal tissues. (B) qRT-PCR was used to evaluate the relative expression of circABCC4 in 47 pairs of prostate cancer and surrounding normal tissues. (C) qRT-PCR analysis of circABCC4 expression patterns in prostate cancer cell lines. (D) Kaplan–Meier survival study of prostate cancer tissues based on circABCC4 expression. *P <0.05 is a significant difference **(Huang et al., 2019).**

The apoptosis protein (XIAP) is an important regulator in human malignancies. Feng et al. discovered that XIAP is a host gene for circRNA0005276 via bioinformatics research. XIAP and circ_0005276 were found to be upregulated in PCs tissues and cell lines. They also confirmed that circ_0005276 had a beneficial effect on XIAP expression. They found that circ0005276 and XIAP increased cell proliferation, migration, and the epithelial-mesenchymal transition functionally. They proved that circ0005276 interacts with FUS binding protein (FUS) to stimulate XIAP transcription on a molecular level **(Feng et al., 2019).**

Circ102004 is found on the minus strand of chromosome 17 and is linked to the well-known oncogene USP22, which is elevated in a variety of cancers **(Piao et al., 2012).** In Si-Tu et al. study the expression of circ-102004 in PCs samples was found to be considerably greater than in comparable normal tissues. Circ-102004 has been found to serve an oncogenic effect in PCs by increasing cancer cell motility and invasion in functional studies. Circ-102004 overexpression was also associated with substantial changes in several signaling pathways, including ERK, JNK, and Hedgehog, all of which have been linked to prostate cancer **(Si-Tu et al., 2019).**

Another study by Kong et al, found that circSMARCA5 which is androgen-induced circRNA, is upregulated when compared to matched normal tissues, it is increased in 5 prostate cancer cell lines and 21 associated prostate cancer tissue samples **(Kong et al., 2017).** Moreover, the expression of circRNA-MYLK (has_circ_0141940) was considerably elevated in PCs tissues and cells using miR-29a as a target. PC cell proliferation, colony formation, invasiveness, migration, and wound healing capacity were all increased by upregulated circRNA-MYLK, whereas circRNA-MYLK significantly decreased the abovementioned viabilities of PCs cells. Upregulation of circRNA-MYLK, on the other hand, significantly reduced PCs cell apoptosis, whereas knockdown of circRNA-MYLK enhanced PCs cell apoptosis **(Dai et al., 2018).**

Several studies have revealed that miR-206 is a negative regulator in the development of human cancers, including prostate cancer **(Yan et al., 2009; Chen et al., 2015).** Prostate cancer cell growth was also shown to be inhibited by miR-206. Lower miR-206 expression by inhibitors restored to function after circ_0057558 knockdown, but higher miR-206 production by mimics restored function after circ_0057558 overexpression. Circ_0057558 regulates cell cycle progression in prostate cancer cells via miR-206, according to these findings **(Ding et al., 2021).**

- ***CircRNAs as PCs oncogenic:***

Circular RNA (circRNA) expression abnormalities are strongly associated with cancer development. As an interesting point, cyclin D1 regulates cyclin-dependent kinase CDK4 and CDK6 and is involved in the transition from the G1 to the S phase of the cell cycle. If the expression of cyclin D1 is dysregulated, that leads to uncontrolled cell proliferation and the development of human malignancies **(Montalto and De Amicis, 2020).**

Yang et al. discovered that circDPP4, a circRNA generated from the DPP4 gene, had dramatically elevated expression in both clinical PCs tissues and PCs cell lines, indicating an oncogenic impact. In vitro gain/loss-of-function investigations revealed that circDPP4 overexpression enhanced PCs cell proliferation, migration, and invasion by sponging miR-195 **(Fig.19)**, whereas circDPP4 knockdown decreased PCs cell proliferation, migration, and invasion **(Yang et al., 2021).** circDPP4 knockdown also inhibited the production of cyclin D1, a well-known oncogene implicated in cell cycle progression, which lowered PCs cell cycle progression (Diehl, 2002).

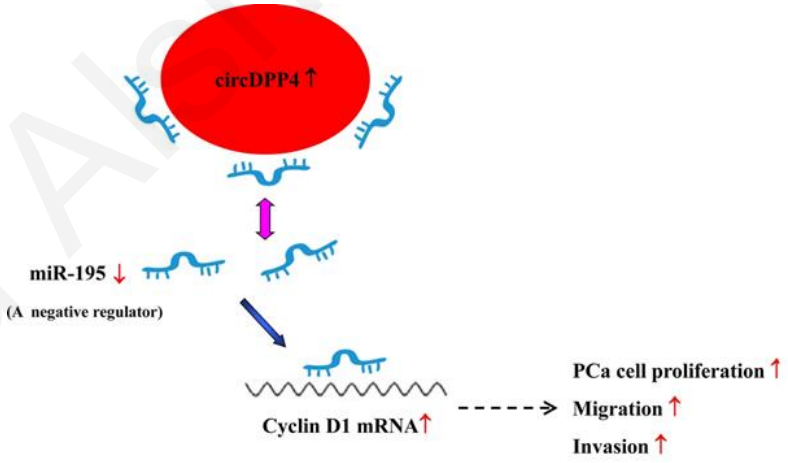


Figure 19: CircDPP4/miR-195/cyclin D1 axis in regulating proliferation, migration, and invasion of PCs cells. **(Yang et al., 2021)**

Ren et al. also discovered that circ 0062019 aided PCs cell malignancy by trapping or sponging miR-1253. MiR-1253, on the other hand, slowed PCs cell growth by modulating NRBP1. In vivo, suppressing circ 0062019 inhibited tumor development. As a general foundation for their research, Circ 0062019 speeds up PCs development by regulating the miR-1253/NRBP1 pathway **(Ren et al., 2021).**

On other hand, similar research conducted by Ren et al. Ding and his team prove that sponging miR-411-5p, circ 0076305 can promote the growth of prostate cancer. They found a link between miR-411-5p and phosphoglycerate kinase 1 (PGK1), and it is known that miR-411-5p directly targeted PGK1 **(He et al., 2020).** The researchers concluded their findings by stating that circ 0076305 acted as a new oncogene that promoted PCs development via the miR-411-5p/PGK1 axis **(Ding, Sun, and Zhang, 2022).**

Moreover, In the diagnosis and therapy of prostate cancer, the androgen receptor (AR) signaling pathway is very important and critical **(Visakorpi et al., 1995).** The possible involvement of androgen-responsive circRNAs in prostate cancer, on the other hand, is unknown. According to Kong et al., there are 3237 androgen-responsive circRNAs. CircNFIA was highly overexpressed in the plasma samples of prostate cancer patients because of all this circ RNA. These findings imply that circNFIA may have a role in prostate cancer development. The CCK-8 experiment revealed that knocking down circNFIA dramatically reduced cell proliferation in prostate cancer, increasing the proportion of cells in the G1 phase and decreasing the number of cells in the S phase to stop cell cycle progression. They concluded that circNFIA may play an oncogenic effect in prostate cancer when used combined **(Kong et al., 2021).**

Circular RNA low-density lipoprotein receptor-related protein 6 (circLRP6) is an oncogene that has been linked to a variety of malignancies **(Xue et al., 2017).** The function and processes of circLRP6 in prostate cancer (PCs) carcinogenesis, on the other hand, are mainly unknown. Qin et al. investigations revealed that circLRP6 may compete with miR-330-5p to prevent the degradation of its target gene NRBP1, while miR-330-5p inhibition reversed circLRP6 knockdowns inhibitory effects on PCs cell growth and metastasis. Furthermore, overexpression of miR-330-5p via NRBP1 inhibited PCs development. The findings showed that circLRP6 increased PCs carcinogenesis and metastasis via the miR-330-5p/NRBP1 axis, implying that circLRP6 might be a viable PCs treatment target **(Qin et al., 2021).**

Another study found that circ 0044516 downregulate miR-29a-3p expression and was negatively related to miR-29a-3p expression levels in prostate cancer, indicating that circ 0044516 was involved in prostate cancer cell survival and metastasis, implying that circ 0044516 may play an oncogenic role in prostate cancer **(Li, Sun and Chen, 2019).**

CircFOXO3, also known as Hsa circ 0006404 is generated from exon 2 of the (FOXO3) gene, and its expression is aberrant in a variety of disorders. Kong et al. discovered that Both PCs tissues and serum samples showed an increase in circFOXO3. In vitro, knocking down circFOXO3 inhibited PCs cell cycle, and proliferation, and promoted cell death. They also showed that circFOXO3 can function as a miR-29a-3p sponge to increase SLC25A15 expression. In PCs, SLC25A15 might counteract the tumor-suppressing effects of circFOXO3 knockdown. They discovered that miR-29a-3p was down-regulated in PCs samples, but that SLC25A15 was overexpressed as compared to normal tissues. Finally, by transcriptional up-regulation of SLC25A15, circFOXO3 works as a miR-29a-3p sponge to demonstrate carcinogenic activity that alters the cell cycle and cell death in PCs **(Kong et al., 2019).**

- ***CircRNA as proliferation promoter of PCs cells:***

CircRNAs can interact with proteins, according to several studies **(Du et al., 2017).** Wang et al. team found circPFKP, a new PCs-related circRNA generated from the Phosphofructokinase, Platelet (PFKP) gene (hsa circ 0006608), was discovered. They then investigated the role of circPFKP in PCs growth and the molecular mechanisms that underpin it. The findings imply that circPFKP increases PCs cell proliferation via interacting with and boosting the enzymatic activity of inosine monophosphate dehydrogenase 2 (IMPDH2) specifically by the cystathionine b-synthase (CBS) domains **(Wang et al., 2022).**

MiR-515-5p has been shown to inhibit cancer cell migration by targeting the MARK4 signaling pathway **(Pardo et al., 2016).** In addition to that, YES1(YES Proto-Oncogene 1, Family Tyrosine Kinase) was directly targeted by miR-515-5p and had an inverse correlation with it **(Garmendia et al., 2019).** In prostate cancer, YES1 expression was shown to be considerably increased **(Chen, Cao, and Feng, 2017).** In recent research by Zhang et al. they were able to prove that circ 0057553 was upregulated considerably in PCs tissues and cells, and circ 0057553 bound to miR-515-5p, which targeted YES1 directly. Surprisingly, circ 0057553 knockdown was partially recovered by miR-515-5p inhibitor, although miR-515-5p overexpression was restored by YES1. In vitro, the circ 0057553/miR-515-5p/YES1 axis-controlled cell survival, proliferation, invasion, and glycolysis. Furthermore, tumor development was seen in vivo **(Zhang et al., 2020).**

Circ 0057558 expression was shown to be higher in prostate cancer tissues and cell lines in a recent study **(Xia et al., 2018).** CircRNAs may absorb miRNAs, lowering the control of miRNAs on their

target genes, according to accumulating research **(Qu et al., 2015).** Ding et al. found by using RNA pull-down analysis that in 22RV1 cells, the circ 0057558 probe only pulled down hsa-miR-206, which has nine paired nucleotides with circ 0057558 **(Fig.20).**

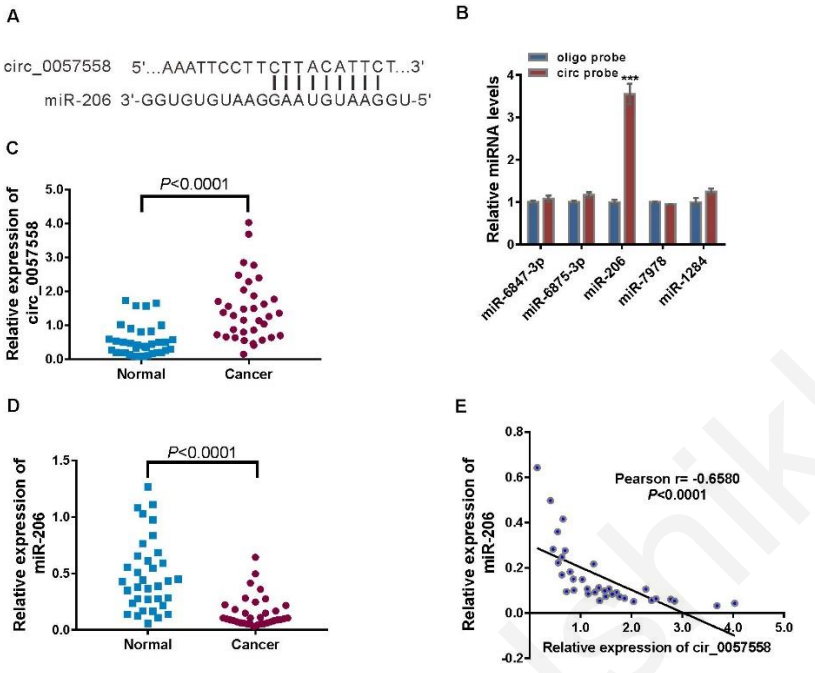


Figure 20: circ_0057558 interaction with miR-206. (A) The putative binding sites of miR-206 and circ_0057558. (B) qRT-PCR analysis of the expression of candidate miRNAs in 22RV1 cells after biotin pull-down assay. (C, D) Expression of circ_0057558 and miR-206 in prostate cancer tissue and adjacent non-tumor tissue. (E) Pearson r analysis showed the correlation between the expression of circ_0057558 and miR-206 in prostate cancer tissues **(Ding et al., 2021).**

Furthermore, in comparison to surrounding non-cancerous tissue, prostate cancer tissues had considerably higher circ 0057558 expressions and significantly lower miR-206 expression. Moreover, the expression of miR-206 in prostate cancer tissues was shown to be adversely linked with the expression of circ 0057558. circ 0057558 was shown to target miR-126, according to the Ding et al. data. On the other hand, they observed that miR-206 inhibitors restored circ 0057558 functions while miR-206 mimics restored circ 0057558 overexpression. USP33, which operates in breast, lung, and colon cancer cells, was chosen as a probable target gene of miR-206 as suggested by miRDB. In 22RV1 cells, miR-206 mimics decreased USP33 mRNA expression, whereas miR-206 inhibitors had the opposite impact **(Yuasa-Kawada et al., 2009).**

The expression of USP33 mRNA in prostate cancer tissues had a negative connection with miR-206 and a positive association with circ 0057558. USP33 was discovered to be a direct target gene of miR-206 in prostate cancer **(Ding et al., 2021).** The results of Ding et al. showed also that

circ_0057558 knockdown reduces c-Myc protein expression and the suppression of USP33 resulted in a significant increase in c-Myc ubiquitination. All to gather, circ_0057558 by sponging miR-206 gives a push to cell proliferation and cell cycle control in prostate cancer cell lines and positively regulates the transcription of the miR-206 target gene USP33 **(Ding et al., 2021).**

Circ-102004 expression was discovered to be considerably greater in PCs samples than in matching normal tissues in research by Si-Tu et al. Circ-102004 is found to play a role in PCs proliferation by increasing cancer cell invasion in the model systems. Circ-102004 overexpression was also associated with substantial changes in several signaling pathways, including ERK, JNK, and Hedgehog, all of which have been linked to cancer **(Si-Tu et al., 2019).**

They discovered that XIAP is a host gene for circRNA0005276 using bioinformatics investigation. XIAP (X-linked inhibitor of apoptosis protein) and circ0005276 were found to be upregulated in PCs tissues and cell lines. They also confirmed that circ0005276 had a beneficial effect on XIAP expression. They confirmed that circ0005276 and XIAP increased cell proliferation and migration on a functional level. They proved that circ0005276 interacts with FUS binding protein (FUS) to stimulate XIAP transcription on a molecular level. To evaluate the critical involvement of XIAP in circ0005276 and FUS-mediated PCs cellular activities, rescue tests were performed. The findings highlighted the mechanism and role of circ0005276 and its host gene XIAP in PCs development and proliferation **(Feng et al., 2019).**

- ***CircRNA as a tumor suppressor and metastasis inhibitor in PCs:***

The mechanism of action of circ-ITCH in prostate cancer growth and development is currently being researched. To address these difficulties, Wang et al. set out to investigate the influence of the circ-ITCH gene on prostate cancer apoptosis and proliferation by identifying circ-ITCH expression in PC cell lines and tissues, as well as evaluate the functional role of circ-ITCH in regulating apoptosis and proliferation. Also, the rise in protein and mRNA expression yields of HOXB13 caused by circITCH overexpression was reversed by miR-17-5p overexpression, according to this study. Furthermore, in prostate cancer tissues, circITCH expression was favorably linked with HOXB13 expression. In prostate cancer, it was discovered that circITCH increased the expression of the tumor suppressor HOXB13 by serving as a sponge for miR-17-5p **(Wang et al., 2019).**

Zhang et al. in recent research were working on circ-0081234 and its effects on the PCs cells, they discovered that the levels of Circ-0081234 were higher in PCs tissues with spinal metastasis (SM) than in primary PCs tissues without SM. PCs cells migrated, invaded, and promoted epithelial-mesenchymal transition (EMT) with the help of circ-0081234. Circ 0081234 knockdown inhibited PCs cell development by controlling miR-1. Interestingly, overexpression of miR-1 inhibited PCs cell growth via inhibiting MAP 3K1. Additionally, circ -0081234 enhanced the amount of MAP 3K1 by sponging miR-1. In vivo, circ-0081234 depletion suppressed tumor development **(Zhang et al., 2021).**

A circRNA called circ-0007494 was recently discovered to be under-expressed in PCs tissues **(Yang et al., 2018).** Zhang et al. discovered that miR-616 mimics reduced the relative luciferase activity of the PTEN-Wt group (known as “mutations," of the PTEN gene on chromosome 10) by looking at the Luciferase activity. Moreover, in PCs cell lines and tissues, circ-0007494 was inhibited. Overexpression of circ-0007494 reduced cell proliferation and invasiveness in vitro and stopped tumor development in vivo. circ-0007494 acted as a "molecular sponge" for miR-616, upregulating PTEN, which is miR-616's target. PTEN knockdown also prevented the tumor-suppressing effects of circ-0007494 overexpression on PCs development in rescue tests **(Fig.21).** This research suggests that has-circ 0007494 inhibits PCs by establishing a negative regulatory network that includes circ-0007494, miR-616, and PTEN **(Zhang et al., 2020).**

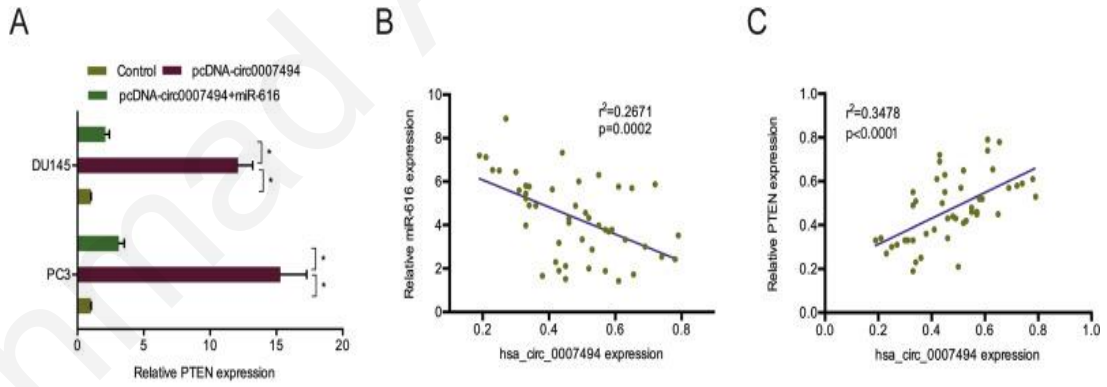


Figure 21: Hsa_circ_0007494/miR-616/PTEN axis in PCs. (A) MiR-616 mimics reversed the impact of hsa_circ_0007494 upregulation on PTEN expression. (B, C) The hsa_circ_0007494 level in PCs tissues was negatively linked to miR-616 levels and positively correlated with PTEN expression **(Zhang et al., 2020).**

According to Xie et al., circSMARCA5 was considerably downregulated in primary and metastatic prostate cancer tissues when compared to normal controls. circSMARCA5 had a suppressive impact on prostate cancer cells' metastasis and proliferation. circSMARCA5 may influence tissue inhibitor of metalloproteinases 3 (TIMP3) expression at the molecular level via interactions with miR-181b-5p or miR-17-3p. Furthermore, lysine acetyltransferase 5 (KAT5) modulated the miR-181b-5p-TIMP3 and miR-17-3p-TIMP3 axis and increased circSMARCA5 biogenesis. These findings showed that targeting the circSMARCA5-miR-181b-5p-TIMP3 and circSMARCA5-miR-17-3p-TIMP3 axis might be a potential method for tumor suppression and PC metastasis inhibition **(Xie et al., 2021).**

Eukaryotic initiation factor 4A-III (EIF4A3) is a kind of protein that is encoded by the EIF4A3 gene in humans (CHAN, 2004). EIF4A3 was identified by Mao et al. and proven as the downstream binding protein of circ_0004296. EIF4A3 expression was shown to be considerably elevated in PCs tissues and was linked to the spread of cancer **(Ummanni et al., 2011).** Circ 0004296 expression was reduced in PCs tissues, blood, and urine, which was related to metastasis in a negative way. Furthermore, in vitro and in vivo gain and loss of function tests revealed that circ 0004296 suppressed PCs cell proliferation, migration, invasion, and epithelial-mesenchymal transition. Circ 0004296 modulated the expression of the host gene ETS1 at the post-transcriptional level **(Mao et al., 2021)**. In another meaning, Circ 0004296 overexpression effectively prevented ETS1 mRNA nuclear export by enhancing EIF4A3 nuclear retention, resulting in ETS1 expression downregulation and PCs metastatic reduction.

CircSLC8A1 is a circular RNA produced by the SLC8A1 gene, had been proved his role in bladder cancer **(Lu et al., 2019),** lung cancer **(Yong et al., 2021),** and cardiac diseases (**Tian et al., 2021).** The role of circSLC8A1 in prostate cancer PCs is still under study. Here, Wang et al. team went in deep and found a common relation between circSLC8A1 and PCs. CircSLC8A1 was shown to be downregulated in PCs tissues and cells, according to the Wang et al. findings. Cell proliferation and migration were both inhibited when circSLC8A1 was reduced. Furthermore, circSLC8A1 interacted directly with miR-21 and acted as a miRNA sponge to halt PCs growth. The circSLC8A1/miR-21 axis regulates cell proliferation, migration, MAPK signaling, and chemokine signaling, according to their functional study. Inconclusions. CircSLC8A1 inhibited tumorigenesis through regulating and sponging miR-21 **(Wang et al., 2021).**

The role of exosomal circHIPK3 in vivo was investigated using a xenograft tumor experiment. Tang et al. found that exosomal circHIPK3 was shown to be higher in PCs patients' serum. In addition to that, exosomal circHIPK3 depletion or overexpression of exosomal miR-212 increased cell death in PCs cells, which was inhibited by miR-212 suppression or BMI-1 (Polycomb complex protein), respectively. BMI-1 was a target of MiR-212, which suppressed its expression. In vivo, exosomal circHIPK3 knockdown also inhibited tumor development. By modulating the miR-212/BMI-1 axis, exosomal circHIPK3 knockdown prevented PCs development **(Tang et al., 2021).**

Each of the previous circRNAs and others represents a potential therapeutic key for prostate cancer and its complications, and it is clear that more studies and research are required in this regard.

- ***Role of circRNA in PCs drug resistance:***

CircRNAs have been shown to have an important role in cancer biology in several studies. CircRNAs control tumor behavior traits including proliferation and migration by a variety of molecular processes including miRNA sponging, transcriptional regulation, and protein interaction. Several studies have recently revealed that they are also heavily engaged in anticancer treatment resistance, starting from traditional treatments (chemotherapy) to immunotherapeutic drugs **(Guarnerio et al., 2016).** Resistance can arise through a variety of pathways, including androgen receptor (AR) copy number expansion, splice variants like AR-V7, and mutations in the AR's ligand-binding domain (LBD) **(Fig. 22).**

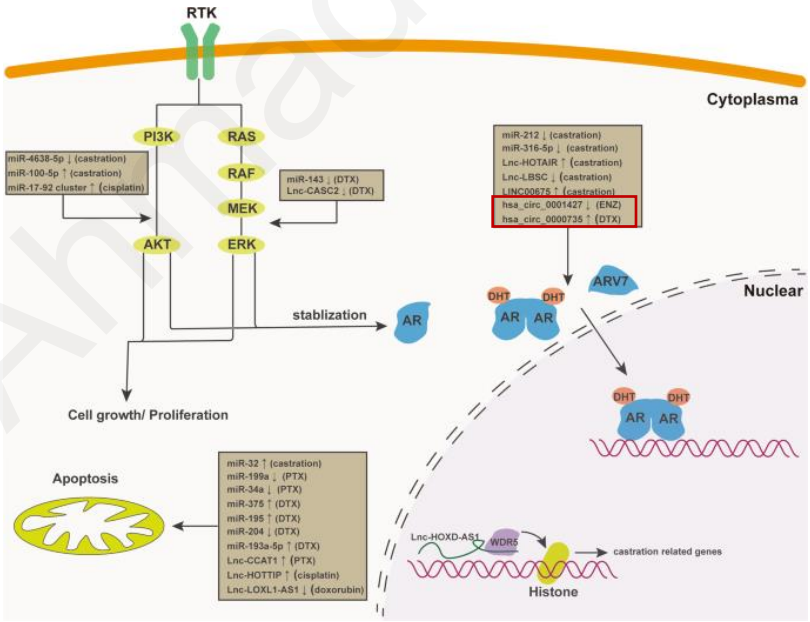


Figure 22: Schematic presentation of noncoding RNAs (include circRNAs) which participate in drug resistance of prostate cancer **(Ding et al., 2021)**.

Androgen deprivation treatment (ADT) that targets androgens/androgen receptor (AR) signals may inhibit prostate cancer cell growth **(Asangani et al., 2014).** Targeting androgens/AR using the antiandrogen Enzalutamide (Enz) or AR-shRNAs increased PCs cell invasion **(Qin et al., 2014)**. As a result of variable endogenous AR transcription, inhibiting androgens/AR signals might result in differential modifications of selective circular RNAs **(Lin et al., 2020).** Negative autoregulation in PCs likely contributes to this prostate tumor outcome, because of differential AR binding to various androgen-response elements (AREs) and discriminating histone H3K4 methylation. Deng et al. made more investigations to reveal that the AR-encoded circRNA-ARC1 may sponge the availability of the miR-125b-2-3p and/or miR-4736, so influencing the metastasis-related PPARγ/MMP-9 signals and thereby altering PCs cell invasion **(Deng et al., 2021)**. Furthermore, the preclinical study of Deng et al. shows that Enz treatment can increase PCs metastasis, which can be suppressed after the knockdown of circRNA-ARC1 with sh-circRNA-ARC1. In another word, working on AR/circRNA-ARC1/miR-125b-2-3p and/or miR-4736/PPARγ/MMP-9 pathways might aid in the development of novel therapeutics for Enz-altered PCs malignancy. **(Deng et al., 2021).**

AR-V7 expression has been linked to enzalutamide resistance. AR-V7 is a shortened version of the AR that lacks the ligand-binding domain **(Antonarakis et al., 2014; Sun and Abdollah, 2015).** Wu et al. looked at the expression of 21 circRNAs that might possibly bind to miRNAs that affect AR-V7, and they discovered that circRNA17 (hsa circ 0001427) could bind to miR-181c-5p, affecting ARv7 activity and thereby PCs cell Enz-resistance (Wu et al., 2019). circRNA17 upregulates miR-181c-5p via preserving its stability, rather than functioning as a sponge. MiR-181c-5p binds to AR-3′-UTR V7's and suppresses its expression. Enzalutamide resistance is altered via the circRNA17/miR-181c-5p/AR-v7 signaling axis **(Wu et al., 2019).**

Xiang et al. found that circUCK2 can alter PCs cells' ability to proliferate and invade. Cell proliferation and invasion are accelerated when circUCK2 is knocked down, whereas cell proliferation and invasion are reduced when circUCK2 is overexpressed. On the other hand, circUCK2 can sponge the miR-767-5p to stop EnzR-C4-2 cells from proliferating and invading, they found also that miR-767-5p can interact with the 3'-UTR of TET1(Tet Methyl cytosine Dioxygenase 1, a Protein Coding gene). When circUCK2 was overexpressed, TET1 was likewise elevated. Furthermore, cutting down TET1 in EnzR-C4-2 cells reversed cell invasion, given that,

circUCK2 reduces cell proliferation and invasion via raising TET1 levels. The in vivo findings revealed that increased circUCK2 expression suppresses EnzR-C4-2 cell proliferation **(Xiang et al., 2019).**

Docetaxel (DTX) is a chemotherapy medication used to treat several types of cancers including prostate cancer. Circ-Foxo3 decreased prostate cancer cell growth and docetaxel resistance, which was linked to circ-Foxo3 suppression of Foxo3 and EMT (Mesenchymal-Epithelial Transition) according to a recent study by Shen et al. Moreover, silencing circFoxo3 expression increased prostate cancer cell survival, invasion, and docetaxel resistance, as well as the beneficial effects of androgen on prostate cancer viability. Circ-foxo3 releases increased chemosensitivity to docetaxel in prostate tumor-bearing mice, but siRNA decreases increased chemoresistance to docetaxel. By targeting Foxo3/Foxo3/EMT pathway it might be a useful tool for finding a possible prostate cancer prognosis and treatment approaches **(Shen et al., 2020).**

In contrast to circ-Foxo3, PCs's resistance to DTX was aided by Circular RNA hsa_circ_0000735. It was upregulated in DTX-resistant PCs tissues and cells **(Fig.23a)** hsa_circ_0000735 works as a sponge for MiRNA-7-5p (miR-7). Mir-7 promote sensitivity to DTX where the expression of miR-7 in DTX-resistant PCs tissues was lower than DTX-sensitive PCs tissues and adjacent normal tissues **(Fig.23b).** Subsequently, Inhibition of hsa_circ_0000735 enhance PCs sensitivity to DTX and prevented DTX-resistant PCs cells from becoming malignant and further inhibited tumor growth. **(Fig.23c) (Gao et al., 2020).** This indicate that hsa_circ_0000735 could serve as a biomarker and therapeutic target for PCs.

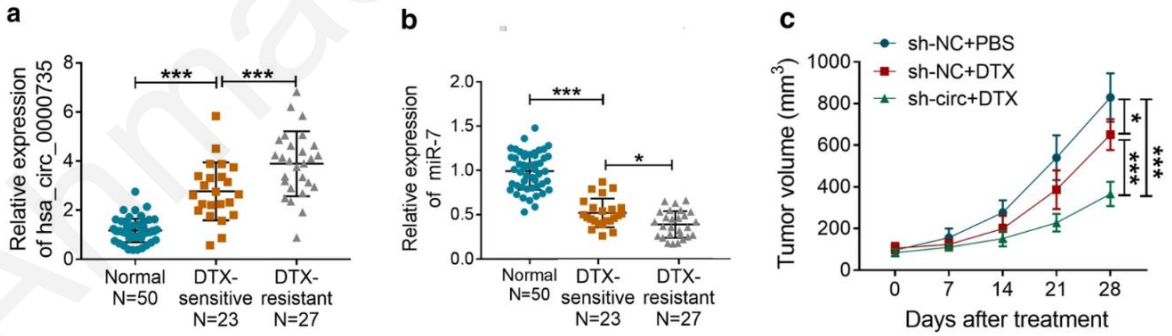


Figure 23: (a) the expression levels of hsa_circ_0000735 in 23 DTX-sensitive PCs tissues, 27 DTX-resistant PCs tissues, and 50 adjacent normal tissues. **(b)** the expression of miR-7 in 23 DTX-sensitive PCs tissues, 27 DTX-resistant PCs tissues, and 50 adjacent normal tissues. **(c)** Tumor volume of mice in sh-NC + PBS **(matching control treated with PBS),** sh-NC + DTX **(matching control treated with DTX),** and sh-circ + DTX **(stable hsa_circ_0000735 knockdown treated DTX)** groups. **(Gao et al., 2020).**

DISCUSSION

Because of their abundance, stability, and disease-specific action, CircRNAs have been discovered as possible biomarkers in cancer **(Dong et al., 2017)**. Bioinformatics problems have made circRNA identification difficult, but the development of new detection procedures and statistical tools has assisted circRNA research, particularly in terms of lowering false-positive detection rates **(Szabo and Salzman, 2016)**. A number of circRNAs have been discovered in PCs and have been suggested as possible biomarkers **(Tucker et al., 2020)**.

There is evidence that circRNAs affect miRNA function by competing for a pool of miRNA binding sites, hence influencing miRNA activity in gene regulation **(Hansen et al., 2013)**. Interestingly, a number of miRNAs found in PCs have been connected to the AR pathway **(Budd et al., 2015; Fabris et al., 2016)**. For each found circRNA with an associated gene, a bioinformatics pipeline may be used to determine miRNA binding sites.

Several techniques for circRNA identification based on high throughput RNAseq datasets have already been developed, although circRNAs do not possess a poly(A) tail **(Jeck and Sharpless, 2014)**. As a result, determining the number of circRNAs necessitated the use of bioinformatic algorithms that searched specifically for circRNAs in datasets obtained from deep sequencing of eukaryotic ribosome depleted RNA **(Salzman et al., 2012)**. Find_circ **(Memczak et al., 2013)**, MapSplice **(Wang et al., 2010)**, CIRCexplorer **(Zhang et al., 2014)**, circRNAFinder **(Westholm et al., 2014)**, and CIRI **(Gao, Wang, and Zhao, 2015)**, make up most of the circRNAs dataset that current researcher's dependent on. Furthermore, because circRNAs lack free ends and are resistant to the exonuclease RNase, this procedure has been used to enrich for circRNAs in RNA-seq data as well as to confirm the circular nature of suspected circRNAs using northern blots or RT-PCR **(Hansen et al., 2013; Suzuki, 2006)**.

CircRNAs have now been identified and considered seriously in a variety of biological domains, primarily to the extensive use of modern technology. RNA-seq and bioinformatics research has revealed the regulatory functions of circRNAs in various vital organs and diseases. The brain, for example, contains hundreds of circRNAs **(Rybak-Wolf et al., 2015)**. Additionally, recent studies

contacted circRNA with multi-diseases, including cancers **(Geng, Jiang and Wu, 2018)**, cardiovascular diseases **(Bayoumi et al., 2018**), and neurological diseases **(Floris et al., 2016)**, and autoimmune diseases **(Xia, Tang, and Wang, 2019)**. CircRNAs have been shown to play important roles in the genesis and progression of cancer, suggesting that they might be used as cancer biomarkers and potential therapeutic targets **(Zhou et al., 2018).** CircRNAs play regulatory functions at the transcriptional and post-transcriptional stages, modulating gene transcription, acting as microRNA (miRNA) sponges, interacting with RNA-binding proteins (RBPs), and translating into a polypeptide **(Conn et al., 2015; Legnini et al., 2017).**

Prostate cancer is the second most often diagnosed cancer in males and the fifth-highest cause of death globally. For primary prevention of prostate cancer, current information on occurrence and outcomes, as well as a better knowledge of the etiology and causative risk factors, are critical **(Panigrahi et al., 2019)**. Elevated plasmatic levels of prostate-specific antigen (PSA), a glycoprotein usually produced by prostate tissue, are used to identify many prostate malignancies.

However, because men without cancer have been identified with increased PSA levels, a tissue biopsy is the gold standard for confirming the existence of malignancy **(Rawla, 2019)**. With the high side effects of biopsies, circRNAs constitute a potential, effective, safe, and accurate biomarker for detecting and tracing prostate cancer **(Xia et al., 2018)**. Circular RNAs have a unique structure that allows them to exist in blood, urine, and tissues. Furthermore, circRNAs have a strong tissue expression specificity, with several circRNAs having considerably higher expression abundance in PCa tissues than their corresponding mRNAs **(Lu, Song and Wang, 2019)**. As a result, circRNAs may be an excellent biomarker for PCa diagnosis.

Lots of studies suggested that circRNAs promote PCs progression **(Tao et al., 2021; Rebbeck 2017; Chen et al. 2019)**. Although some of the results of these studies were contradictory, like CircFoxo3 which is abundant in both PC tissues and serum. It enhances PCs development by serving as a sponge for miR-29a-3p and upregulating the expression of SLC25A15 **(Kong et al. 2020)**. At the same time, it's been claimed that circFoxo3 can slow the progression of prostate cancer **(Shen et al. 2020)**. CircFoxo3 is low expressed in high-grade PC, and low expression of circFoxo3 has been found in studies to enhance PC advancement and chemical resistance to docetaxel by promoting EMT, indicating that circFoxo3 limits PC progression **(Shen et al. 2020).** CircRNAs' key strategy for regulating downstream targets is their role as miRNA sponges that

control downstream gene expression **(Ng, Mohd Mohidin, and Shukla, 2018).** Moreover, miRNAs such as circZNF609, circ-102004, circMBOAT2, and cirITCH, which engage in AMPK, ERK/JNK/Hedgehog, PI3K/AKT/mTOR, and Wnt/-catenin pathways, respectively, control several cancer-related signal pathways through circRNAs **(Jin et al., 2019; Si-Tu et al., 2019)**. CircRNAs also have the ability to bind to proteins and influence their activities expression **(Ng, Mohd Mohidin and Shukla, 2018)**. When circRNAs are found in the nucleus, they can bind to RBP and regulate the expression of their parental genes by attaching to their promoters **(Du et al., 2017)**.

PCa is a hormone-dependent malignancy in which cancer cells primarily depend on lipid oxidation for development **(Deep and Schlaepfer, 2016)**. Lipid metabolism anomalies have been found in PCa patients, and the lipid metabolism process is one of the main targets of PCa cell androgens because it is strongly associated with PCa cell growth, survival, and treatment resistance **(Swinnen et al., 1996)**. Moreover, androgen promoted the expression of circRNA in PCa cells in a concentration-dependent manner according to a recent study **(Jiang et al., 2020).**

CircRNA according to several studies, has proven its work as an oncogene, and in the case of prostate cancer as well. Yang et al. reported that circDPP4, a circRNA derived from the DPP4 gene, exhibited significantly increased expression in both clinical PCs tissues and PCs cell lines, implying an oncogenic effect **(Yang et al., 2021)**. Circ 0062019 promotes the formation of PCs via controlling the miR-1253/NRBP1 pathway **(Ren et al., 2021)**. Other researchers found that circ 0076305 operated as a novel oncogene that boosted PC growth via the miR-411-5p/PGK1 axis, proving that certain circRNA may act as oncogenes **(Ding, Sun, and Zhang, 2022)**, and in many other studies, they were able to prove this theory **(Kong et al., 2021; Xue et al., 2017; Qin et al., 2021; Li, Sun and Chen, 2019; Kong et al., 2019).**

In an opposite case, the researchers were able to prove the interference of circRNAs in the process of inhibiting prostate cancer and preventing its spread, either by absorbing mRNA, like miR-17-5p **(Wang et al., 2019)**, miR-1 **(Zhang et al., 2021)**, miR-616 **(Zhang et al., 2020)**, or by targeting the circRNA-miRNA axis's **(Xie et al., 2021; Wang et al., 2021)**, or even by modulating the parental genes to down-regulate some proteins **(Mao et al., 2021)**. Also, the knockdown of some circRNAs suppresses prostate tumors **(Tang et al., 2021)**.

On the other hand, many studies have taken care of the effect of circRNAs on the therapeutic regimens used in the treatment of prostate cancer, and it seems that the circRNAs have a clear and effective effect on some anticancer used in the treatment of PCs, as is the case in Enzalutamide. Wu et al. investigated the production of 21 circRNAs that may bind to miRNAs that control AR-V7, which has been connected to enzalutamide resistance, and reported that circRNA17 (hsa circ 0001427) might bind to miR-181c-5p, altering ARv7 activity and hence PCs cell Enz-resistance **(Wu et al., 2019)**. Docetaxel which is a chemotherapy medication used to treat prostate cancer also has resistance reported connected to circRNAs, knockdown the expression of Foxo3 boosted prostate cancer cell survival, invasion, and resistance to docetaxel **(Shen et al., 2020)**. Additionally, hsa_circ_0000735 works like a sponge for MiRNA-7-5p (miR-7), and Mir-7 promotes sensitivity to DTX, so inhibition of hsa_circ_0000735 enhances PCs sensitivity to DTX and prevented DTX-resistant PCs cells from becoming malignant and further inhibited tumor growth **(Gao et al., 2020)**.

So far, more than 400 000 distinct circRNAs have been discovered, more than double the number of linear transcripts. However, they don't completely understand the control of circRNA biogenesis and it's functional roles **(Vo et al., 2019)**.

With this large number of circRNAs discovered and the good number of studies on the relationship of prostate cancer with circRNAs, the results obtained so far are no more than laboratory results, not beyond the experimental laboratory phase (in vitro or in silico) to the clinical phase (in vivo). Whereas the use of circRNAs did not go beyond being a biomarker, but as a potential treatment (clinical treatment) it is still under research and investigation.

In this research, the light was shed on circular RNA in general and its relationship with prostate cancer in particular, and with the in-depth research that was done on this topic, many points and question marks have emerged that must be addressed, and although the field of circulating RNA and its relationship with prostate cancer is fairly recent, It is necessary to mention some points that should be taken into account, including:

According to circRNAs biogenesis, the mechanism of transfer of circRNAs from the nucleus to the cytoplasm has not been mentioned, which that indicates, the exportation from the nucleus to the cytoplasm is still via an unknown process. In addition, a question arises here, why is the concentration of circRNAs high in the cytoplasm at the expense of the nucleus, there is a possibility

that the area of biological processes inside the nucleus is narrow or insufficient for the many functions played by circRNAs, which is the discovery of it continuing until this moment, or there is the presence of some biological elements necessary for the functions of circRNAs, which push this molecule to move to the surrounding plasma, this part needs to be highlighted more.

Several circRNAs have been studied in many PCa studies. Even though the study methodology and samples are similar, various mechanisms of action have been found. The ideal explanation is that during the same illness, the same circRNA works on different miRNA molecules with synergistic effects, but it's also important to keep in mind whether particular experimental data can genuinely lead to definite conclusions, in general, it needs more research and investigation to find out the real reason behind the complete difference in the results for the same studied element, this is on the one hand. On the other hand, most of the studies and research conducted lacked mechanisms and tools that would verify the validity of the results and ensure that there are no false-negative results or even false-positive results.

Many studies have been used bioinformatics analyses and miRNA rescue experiments alone, as a mean base for the study, in this case, there is a big possibility for the indirect effect and a lot of interaction between circRNAs and miRNAs, indicating a need for more accurate methods when investigating their relationships to avoid fake results.

Several previous studies have proven the ability of circRNAs to encode proteins, but studies in this direction are still relatively few or almost non-existent. The presented studies focused on the role of circRNAs in the sponge mechanism or axis/pathways of protein-coding, not on the coding of proteins directly by circRNAs. It is known that the field of proteomics is rather complex and considering that circRNAs are still an active research spot so far and the dimensions are not fully understood, this could represent a reasonable reason for ignoring studies of the effect of circRNAs on coding proteins.

There has been no substantial investigation into the use of circRNAs in the treatment of PCa. There has been some study on the function of circRNAs concerning chemotherapy, radiation, and the Enz treatment of PCa in prior research that focused on treatment resistance. However, the mechanics behind this are still many questions. Besides that, the circRNAs function in autophagy, particular cell-signaling pathways, the tumor microenvironment, tumor stem cells, tumor cell metabolism, and homologous recombination DNA repair of gene mutations for treatment

resistance research should all be investigated further. The impact of hormones on the regulation mechanism of circRNAs and other factors, such as DNA methylation or RNA-binding protein, would be extremely useful.

Recent research has suggested that unique circRNA exonic sequences influence immunity and that endogenous m6A alteration dampens innate immunity in particular **(Chen et al., 2019)**. Mice were given circ-FOREIGN, ovalbumin, and ovalbumin-expressing B16 melanoma cells, one after the other. According to the findings, mice given circ-FOREIGN had decreased tumor development and nearly doubled overall survival **(Chen et al., 2020)**. If this can be applied in the case of prostate cancer, we are in front of a possible novel drug for it, and this point needs further research and study.

CircRNA interactome and single-cell profiling are two examples of projected advancements in the area, allowing for a higher resolution of cellular distinctions and a better understanding of a cell's activity in its milieu. The growing importance of circRNA in health and diseases implies that not only will there be more uses in the future, but more specialized circRNA instruments will be developed to fulfill these demands.

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