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microRNA-205 in prostate cancer: Overview to clinical translation

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Abstract

Prostate cancer (PrCa) is the most common type of cancer among men in the United States. The metastatic and advanced PrCa develops drug resistance to current regimens which accounts for the poor management. micro-RNAs (miRNAs) have been well-documented for their diagnostic, prognostic, and therapeutic roles in various human cancers. Recent literature confirmed that microRNA-205 (miR-205) has been established as one of the tumor suppressors in PrCa. miR-205 regulates number of cellular functions, such as proliferation, invasion, migration/metastasis, and apoptosis. It is also evident that miR-205 can serve as a key biomarker in diagnostic, prognostic, and therapy of PrCa. Therefore, in this review, we will provide an overview of tumor suppressive role of miR-205 in PrCa. This work also outlines miR-205′s specific role in targeted mechanisms for chemosensitization and radiosensitization in PrCa. A facile approach of delivery paths for successful clinical translation is documented. Together, all these studies provide a novel insight of miR-205 as an adjuvant agent for reducing the widening gaps in clinical outcome of PrCa patients.

Keywords

Prostate cancer; microRNA; Chemosensitization; Chemotherapy; Radiation; Biomarker

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Declaration of Competing Interest

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

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1. Introduction

Prostate cancer (PrCa) is the most common type of cancer and second leading cause of cancer related deaths among men in the United States [1]. The prostate is an organ in the male reproductive system tasked with the job of creating fluid to maintain and aid sperm in their transport. The prostate functions normally in men until they become much older [2]. In some cases, cells in prostate gland start to grow (replicate at a rapid rate), giving rise to PrCa. Prostate cancer is caused by either the lack of tumor suppressors or the over production of oncogenes in the prostate epithelium cells. Majority of prostate cancers fall under adenocarcinomas while few other types of prostate cancer include, sarcomas, small cell carcinomas, neuroendocrine tumors, and transitional cell carcinomas [3]. Most of prostate cancers grow slowly and are confined regionally within the prostate gland. Such cancers may be treated efficiently if diagnosed early. Some prostate cancers grow and spread to bones, lungs, lymph nodes, adrenal gland, and liver *via* lymphatic system or blood stream [4]. These tumors metastasize for years within the prostate before most physicians are able detect them [5].

Blood prostate-specific antigen (PSA) test and physical digital rectal examination (DRE) are two main tools for detecting/screening prostate cancer [6]. However, PSA testing (normal reference range 1 to 1.5 ng/mL and cutoff point 4 ng/mL or higher) has been debatable because of its inability to diagnose cancer in all cases as around 15% of men showing PSA levels under 4 ng/mL were reported to have prostate cancer, and many cases (~ 70% men) with negative prostate biopsies showed PSA levels over cutoff up to 10 ng/mL [7,8]. In addition, factors such as certain medications and medical procedures, enlarged prostate and prostate infections affect PSA levels. Therefore, in lack of an optimal cancer diagnosis strategy and as cancer continues to evade treatment, there is an ongoing battle to find newer ways to diagnose and treat prostate cancer more effectively.

In recent years, liquid biomarkers such as exosomes, tumor educated platelets, circulating tumor cells, cell free nucleic acids, long non-coding RNA, and miRNA, have gained much interest among researchers and physicians [9]. Among these, utilization of microRNAs (miRNAs) is a prominent strategy to aid cancer screening, diagnosis, and adjuvant therapy [10]. microRNAs are single stranded non-coding molecules that facilitate the transcription process. While miRNA is most often seen in the base pairing of RNA, they also play important roles in numerous cellular processes such as cellular proliferation and metastasis [11]. miRNAs are suggested to have differential expression in normal and cancer cells, and also in various stages of cancer development and metastasis [12]. The expression pattern of a miRNA indicates its role as oncogene or tumor suppressor in a particular cancer [13]. In this regard, microRNA-205 (miR-205) is one such molecule that has cancer specific expression. For instance, miR-205 is an oncogene in cervical [14] and ovarian [15] cancers while also acting as a tumor suppressor in breast [16] and prostate [17] cancers.

Human miR-205 was first recognized in a computational study and thought to be a highly conserved microRNA [18]. It was only after 2010 when researchers started to show great interest in studying miR-205 (Fig. 1 A). Scientific literature suggests that miR-205 has cancer specific expression in different cancers (Fig. 1 B). miR-205 is upregulated in bladder

[19], ovarian [20], cervical [21], endometrial [22], head and neck [23] and lung [24] cancers but, is downregulated in breast [25,26], prostate [27,28], liver [29], glioblastoma [30], melanoma [31], and renal cancers [32]. However, in pancreatic and colon cancers, expression, and role of miR-205 are highly debatable due to available mixed reports [33–36].

miR-205 is known to play a crucial role in multiple cellular processes *via* targeting various downstream signaling molecules (Fig. 2). An integrated analysis of miR-205 and its associated target genes were identified in landscape and cellular networking pathways in stage-specific prostate cancer (early stage – ERBB3, BCL2, VEGFA, PTEN; advanced stage – VEFGA, PTEN, AR, ERBB3, E2F1; and castration resistance prostate cancer – AR, PTEN, ERBB3) [37,38]. Another pathway network of genes targeted by miR-205 was confirmed to VEGFA, PRKCE, BRBB3, CLTC, ESRRG, MED1, DDX5, SORBS1, ACSL1, NFAT5, INHBA, and IL24 [39].

Wang *et al.* [40] reported that miR-205 inhibits breast cancer cell proliferation and activates apoptosis by reducing Bcl-2 and Bax proteins *via* directly targeting HER3. In melanoma cancers, miR-205 exerts apoptotic and anti-cell survival properties through inhibiting E2F1 and phosphorylation of its downstream targets AKT, BAD, and Caspase 9 [31]. Another study [41] revealed that this microRNA binds to YAP1 protein and inhibits cell growth, migration, and invasion in glioma cells. YAP1 is a known regulator of cell proliferation and migration in many cancers [42]. In addition to cell proliferation and apoptosis, miR-205 has been extensively researched as a regulator of epithelial to mesenchymal transition (EMT). EMT is an essential event in cancer progression and responsible for cancer metastasis [43]. Loss of E-cadherin (epithelial marker) during EMT is the key feature of this process which further directs upregulation of N-cadherin (mesenchymal marker) [44]. Zinc finger E-box Binding homeobox1/2 (ZEB1/2) are two known regulators of E-cadherin and miR-205 directly targets these molecules [45]. Additionally, overexpression of miR-205 was shown to alter the expression of key EMT markers such as MMP2, MMP9, VEGF, LPR1, ZEB1/2, E-cadherin, and N-cadherin, and as a result controls cellular migration and invasion in several cancers [27,46–49]. Altogether, current literature advises that miR-205 involved in multiple cellular processes (Fig. 3). miR-205 influencing on various cellular and molecular events in the prostate cancer pathogenesis is discussed in detail in section 4.

Table 1 documents the review articles published on miR-205 exerting its clinical and pathological importance in cancer. However, till date there is no review article published that is focused on discussing miR-205's role in prostate cancer. Thus, considering these valuable insights for miR-205 as a potent biomarker in cancer progression and cancer related phenotype changes, this review will focus on its importance in prostate cancer as this cancer has high tendency to metastasize to many vital organs such as lung, liver, or even bones [50]. This review will provide an extensive overview on miR-205's functions and its potential to become a lead molecule to fight against prostate cancer.

2. miRNAs in prostate cancer

Several miRNAs that are involved in prostate cancer pathogenesis have been reported to be deregulated, affecting many processes at molecular and cellular levels [60]. Various studies have confirmed numerous miRNAs that are downregulated in PrCa, mainly, miR-22, miR-24, miR-26a, let-7b, let-7c, let-7e, miR-100, miR-125a, miR-125b, miR-199a, miR-205, miR-221, miR-222, miR-27b, miR-29a, miR-130a, miR-133a, miR-133b, miR-143, and miR-145 [61–63]. miRNAs that have an over expression in PrCa, are documented as let-7a, miR-20a, miR-20b, miR-21, miR-25, miR-32, miR-93, miR-95, miR-96, miR-103, miR-106a, miR-106b, miR-130b, miR-141, miR-148a, miR-182, miR-183, miR-191, miR-200b, and miR-200c [62–64].

These deregulated miRNAs participate in PrCa tumorigenesis *via* influencing many cellular functions [65,66]. Uncontrolled cell growth is the hallmark for cancer initiation and progression which is often resulted from disturbed cell cycle and inhibited apoptosis. Overexpressed miR-21 was reported to hinder apoptosis through directly inhibiting PTEN, a known tumor growth suppressor [67,68]. miR-888 is another oncogene that promotes prostate cancer growth by downregulating retinoblastoma like protein 1 (RBL1). RBL1 directly binds to transcriptional factors E2F and regulates cell cycle progression from G1 to S phase [69].

Self-renewing cancer stem cells play a crucial role in prompting cell proliferation, thus, accelerating tumor progression. Several miRNAs including let-7 family, miR-141, and miR-143 were found to regulate prostate cancer cell stemness [61–63,70]. EMT is a classic characteristic of PrCa metastasis. To date, many miRNAs such as miR-141, miR-200 family, and miR-205 have been evolved as key regulators of EMT process by activating epithelial markers (E-cadherin and β-catenin) and suppressing mesenchymal markers (ZEB1 and vimentin) [29,62,71,72].

3. Transcriptional regulation of miR-205 in prostate cancer

Expression of miR-205 was reported to be regulated by epigenetic modulations and through transcriptional factors (Fig. 4).

Epigenetic modifications such as DNA methylation (CpG, Cytosine [phosphodiester bond] Guanine) and histone acetylation play a critical role in miRNA transcription and gene expression. During the epigenetic modifications, DNA methyltransferase (DNMT) and histone deacetylases (HDACs) deactivate the chromatin which further leads to suppressed transcription of genes [73]. Epigenetic modulation of miR-205 has also been reported as CpG DNA methylation sites were found to be at the direct upstream region of MIR205HG first exon and in miR-205 locus [74,75]. In prostate cancer, DNA hypermethylation and H3K9 (Lysine 9 of Histone 3) deacetylation of miR-205 locus were reported to suppress miR-205 expression leading to drug resistance and poor prognosis [74,76]. According to another report, H3K27me3 (Lysine 27 of Histone 3) and H3K4me3 (Lysine 4 of Histone 3) trimethylation in miR-205 locus also negatively regulate (repress) the expression of miR-205 [77]. However, it was noticed that epigenetic modulation is not the only cause for

miR-205 repression in prostate cancer, there are several other key molecules that are crucial for transcriptional regulation of this micro-RNA. Studies have shown that transcriptional factor, p53 binds to p53REs (p53 Responsive Elements) in miR-205 upstream region and enhances miR-205 transcription and thus, mutations in p53 and its inability to interact with p53REs result in suppressed miR-205 [78]. In fact, mutant p53 is reported to repress p63, leading to reduced miR-205 [79]. Two other known transcriptional factors, p63 and p73 structurally resemble with p53, therefore can bind to p53REs in the upstream region of miR-205 and modulate its transcriptional activity [80,81]. According to several reports, p63 and ΔNp63α (isoform) interact with p53REs, leading to upregulation of miR-205 [79,82]. p73 also acts like p63 and induces miR-205 however, its isoform ΔNp73 disturbes the activity of p73 which results in suppressed miR-205 expression [81]. Specificity protein 1 (Sp1) is another transcriptional factor that binds to Sp1REs (Sp1 Responsive Elements) at the immediate upstream region of MIR205HG and upregulates the transcriptional activation of miR-205 after irradiation mediated DNA damage which in turn activates PTEN-PI3K-Akt signaling and promotes radio resistance in esophageal squamous cell carcinoma [83]. Redox sensitive transcriptional factor, Hypoxia Inducible Factor-1 α (HIF-1α) was also indicated to represses miR-205 expression *via* binding with its REs (Responsive Elements) at the proximal upstream region of MIR205HG, further facilitating the elevation of ZEB1/2 and PKCε to ultimately promoting EMT in PrCa [84]. TWIST1, a widely studied EMT promotor, was also found to be directly interacting with premiR-205 region and suppressing its transcription in invasive bladder cancer [75].

4. Role of miR-205 in prostate cancer

Therapies for localized prostate cancer is available, however, metastatic prostate cancer is still difficult to treat [85]. Mortality related to prostate cancer is often contributed by the metastatic state of disease where cancer has progressed to an androgen-independent stage from an androgen-dependent [86]. An analysis of 27 miRNA array and miRNA sequencing dataset revealed that miR-205 was significantly downregulated in PrCa and bone metastatic samples *via* negatively targeting CDK1 [87].

miR-205 is involved in regulating the progression of PrCa through EMT signaling [88]. Gandellini *et al.* [89] reported that overexpression of miR-205 in PrCa facilitated mesenchymal-to-epithelial transition (MET) and resulted in upregulation of E-cadherin leading to reduced cellular migration and invasion *via* downregulating E2F1, ErbB3, N-chimaerin, ZEB2, E2F5, and protein kinase C epsilon [PKCε] (known EMT markers). Another report [90] suggested that overexpression of miR-205 in PrCa cells targeted IL-24 and IL-32, two known tumor suppressors, leading to decreased cell growth, migration, and invasion as well as induced apoptosis and cell cycle arrest. Tucci and group [79] has also shown that restoration of miR-205 targets ZEB1 and vimentin which further inhibits lung metastasis of PrCa in a xenograft mouse model. miR-205 initiates cell growth inhibition, induces cell apoptosis, and cell-cycle arrest by targeting BCL2 (anti-apoptotic gene) [91], androgen receptor(AR) and Mitogen Activated Protein Kinase (MAPK) signaling pathways [92]. This evidence reveals the significance of miR-205 in cellular and molecular functions in prostate cancer which will later be discussed in detail in this review.

4.1. miR-205 expression

miR-205 has been established as a differentially expressed key biomarker for breast, glioblastoma, liver, endometrial, lung, and prostate cancers [41,89,93–96]. PSA is a known predictor for diagnosis and screening of prostate cancer. However, PSA expression increases in prostatic hyperplasia and prostatitis patients as well. Herein, its specificity for early prostate cancer diagnosis is poor [97]. Therefore, biomarkers with higher specificity for early diagnosis and screening for PrCa are urgently required. A separate study [98] established that expression of miR-205 was significantly lower in patients with prostate cancer than that of prostatic hyperplasia. A cohort of 88 prostate cancer patients and 84 prostatic hyperplasia patients (as controls) demonstrated that miR-205 was significantly downregulated in the prostate cancer group than prostatic hyperplasia group [98]. If the Gleason score is between 8 to 10, PrCa is more likely to metastasize [99]. In this study, patients with prostate cancer having Gleason score above 7 have shown statistically lower expression of miR-205 than that of with score below 7. Similarly, early PrCa metastatic stage (M0) patients had significantly higher relative expression of miR-205 than distant metastatic stage ones (M1). Moreover, high-risk prostate cancer group also demonstrated statically significant lower relative expression of miR-205 than that of the other two groups (low-risk and medial-risk) [98].

Considering the tumor suppressive role of miR-205 in prostate cancer, Gandellini and colleagues [28] evaluated the physiological function of miR-205 in normal prostate to understand its expression-based role in prostate cancer progression. In this study, miR-205 was found to be involved in ΔNp63α and ZEB1 network which is important for basement membrane maintenance and tumor cell invasion. Basement membrane is a protective extracellular matrix layer that surrounds normal prostate and acts as a barrier between epithelial and mesenchymal cells/tissues. Therefore, disintegrated and/or discontinued basement membrane is required for tumor cell invasion leading to epithelial to mesenchymal transition/metastasis [100]. It was observed that miR-205 is highly expressed in basal cells [101]. This study revealed the molecular mechanism by which miR-205 regulates and/or maintains basement membrane deposition. ΔNp63α was found to be binding to 5’UTR promoter region of miR-205 and increasing its transcription. However, miR-205 was shown to affect proteasomal degradation of ΔNp63α, thus, limiting the amount of ΔNp63α protein post-transcriptionally. Further, miR-205 was silenced in RWPE-1 (normal prostate epithelial) cells which resulted in decreased gene and protein levels of laminin-332 complex and its receptor integrin-β4 (basement membrane components). Conversely, overexpression of miR-205 in PC-3 and DU-145 prostate cancer cells (these cells do not express miR-205 natively) [89] led to enhanced expression of laminin-332 complex. Moreover, overexpression of miR-205 in PC-3 cells reversed the invasive phenotype into normal like acinar morphology/structure as shown in 3-dimensional culture. Herein, suggesting the importance of miR-205 in basement membrane deposition and controlling tumor invasion *via* targeting epithelial to mesenchymal transition [28].

*mir*Vana miRNA Bioarray analysis confirmed a differential expression profile of a variety of miRNAs in WPE1-NA22 and WPE1-NB26 cells [102]. From these tested 471 human miRNAs, it was found that miR-205 (−93.1), miR-31 (−77.1), miR-24 (−35.3), miR-27a

(−33.6), and miR-22 (−26.0) were significantly decreased in WPE1-NB26 cells compared to WPE1-NA22. Further real-time PCR data demonstrated a downregulation pattern of miR-205 in early and advanced prostate cancer cell lines [102] (Fig. 5 A). The miR-205 expression levels were noticed as: RWPE-1 > WPE1-NA22 > PC-3 > WPE1-NB14 > WPE1-NB11 > WPE1-NB26 > LNCaP/22Rv1/VCaP/DU-145. However, there was no miR-205 content identified in LNCaP, 22Rv1, VCaP, and DU-145 cells.

Investigation from Hagman *et al.* [103] has validated the expression levels of miR-205 in different prostate cell lines as well namely, DU-145, PC-3, LNCaP, 22Rv1, VCaP, and PNT2. *In vitro* findings were in correlation with patients' tumor tissues cohort results. All prostate cancer cell lines were lacking miR-205 expression, however, PNT2 (normal immortalized) cells showed high levels of miR-205 expression. It is also important to note that miR-205 was predominately expressed in the cytoplasm of epithelial cells in normal tissues (non-cancerous) as evident by *in situ* hybridization analysis (Fig. 5 B). This study further delineated the role of miR-205 in a cohort of 49 PrCa patients and 25 normal control subjects. A comparative qRT–PCR study performed on FFPE prostatic tissues indicated that patients with metastases had statistically significant lower levels of miR-205 than in patients without metastasis (Fig. 5 C, i). Overall survival was found to be higher in patients with high miR-205 expression than those with low expression (Fig. 5 C, ii). The expression of miR-205 was found to be downregulated more in castration resistant patients (Failed androgen ablation therapy) than in androgen naïve patients (Fig 5 C, iii). Further, results from this cohort suggested that miR-205 was highly expressed in benign prostatic hyperplasia (BPH) samples (median expression - 1.67) and its expression decreased as cancer grade progressed as per WHO (Grade I - 0.77, Grade II - 1.03, Grade III - 0.64).

Another study also revealed the similar expression status of miR-205 in PrCa cell lines and tumor tissue samples [90]. Relative expression of miR-205 was downregulated in all tested PrCa cell lines regardless of their androgen status; LNCaP (androgen dependent), PC-3 and DU-145 (androgen-independent) when compared to normal non-malignant RWPE-1 cells which showed high levels of miR-205 as confirmed by qRT-PCR. *In situ* hybridization staining with digoxigenin (DIG)-labeled locked nucleic acid based miR-205 also exhibited high fluorescence intensity/signal in RWPE-1 cells while other three prostate cancer cell lines did not present any signal for miR-205. Additionally, data from tumor and normal tissue samples represented the same information where BPH samples (n = 24) had highly expressed miR-205 and tumorous samples (n = 23) had undetectable expression.

4.2. miR-205 as a tumor suppressor

In order to exert tumor suppressive function of miR-205, Majid et al. [90] overexpressed PC-3 prostate cancer cells with miR-205 for 72 hours and evaluated its effects on other tumor suppressive genes. A marked increase in relative mRNA expression levels of IL-24 and IL-32 was noticed (8 and 5-fold, respectively) with miR-205 restoration when compared with control miR group, and results were similar with protein levels too. IL-24 (MDA-7/IL-24) is a known tumor suppressor gene in many cancers including breast [104], melanoma [105], lung [106], and others [107,108]. IL-24 plays a crucial role in apoptosis induction, immune response stimulation, radio sensitization, and angiogenesis suppression [108–110].

Similarly, IL-32 is also a known tumor suppressive cytokine with known functions in apoptosis [111] and inflammation regulation [112]. It was observed that these two genes are direct target of miR-205 as analyzed by luciferase reporter assay. This activity of miR-205 to induce the expression of tumor suppressor genes has the therapeutic potential for PrCa which further delineates its tumor suppressive function in this cancer.

In high-risk prostate cancer, uncontrolled expression of Bcl-2 (anti-apoptotic) pathway is known to regulate cell survival and evasion from apoptosis, ultimately leading to poor prognosis in addition to increasing the risk of cancer recurrence [113]. In PrCa, Bcl-2 was found to be a direct target of miR-205. Bcl-2 was inversely correlated with miR-205 expression as levels of Bcl-2 increased with cancer grade progression. Moreover, miR-205 upregulation in PC-3 and LNCaP prostate cancer cell lines reduced cell viability, induced apoptosis, and chemosensitization of these cells towards doxorubicin and cisplatin which otherwise was hindered by high Bcl-2 expression in these metastatic cells, supporting tumor/cancer suppressive function of miR-205 [91].

Other studies also support the tumor suppressive role of miR-205 in PrCa as it regulates epithelial-to-mesenchymal transition which in turn suppresses cancer cell migration/invasion *via* inhibiting many oncogenes supporting cancer cell metastatic mainly ZEB1, ZEB2, PKCε, and N-cadherin [27]. A report further validates that miR-205 has the potential to block the ZEB1 protein. ZEB1 protein is commonly known as a gene that represses IL-2 gene expression which is a key signaling in the immune system. Further investigation, however, shows ZEB1 is responsible to increase tumor growth by repressing E-cadherin. E-cadherin is a tumor suppressor that is essential for the progression/transition of healthy cells to cancer cells. In fact, the loss of E-cadherin is responsible for the transition of benign cells to metastatic cells [57,114,115]. A study done by Drake and colleagues [115] isolated aggressive TEM4-18 cells from prostate cancer tissues which was able to initiate EMT transition through an upregulation of ZEB1. The upregulated of ZEB1 along with the loss of E-cadherin levels resulted in increased EMT transition.

Another study [116] also supports tumor suppressive role of miR-205 where ectopic expression of this miRNA in DU-145 cells injected in xenograft mouse model resulted in reduced tumor growth, supporting their *in vitro* findings with suppressed cell proliferation, clonogenicity, cell-cycle progression, migration, invasion, and induced apoptosis (done in PC-3 and DU-145 cell lines). These findings are mediated through the downregulation of an oncogene c-SRC by miR-205. In PrCa, miR-205 directly targeted c-SRC and inhibited its expression, suggesting the tumor suppressive role of miR-205 in prostate cancer. c-SRC plays a crucial role in cancer cell proliferation, morphology, adhesion, invasion, migration, apoptosis, and survival, and often c-SRC expression has been linked with advanced stages of cancer [117–121].

4.3. Cancer cell signaling pathways

miR-205 has been shown to target multiple signaling pathways and different molecules involved in these pathways. Cellular function that a miRNA modulates is dependent on what signaling pathways and/or genes are targeted by that miRNA. Therefore, this section will highlight some of the miR-205 targeted molecules and their associated pathways. A

study by Wang and associates [116] demonstrated that miR-205 suppressed c-SRC (its phosphorylation as well) and its downstream signaling molecules/pathway mainly FAK, p-FAK, ERK1/2, p-ERK1/2, c-MYC, and Cyclin D1 which further led to inhibited prostate cancer cell/tumor growth, migration, invasion, and cell cycle. Multiple other reports also indicated that c-SRC is associated with advanced/metastatic stages of cancer and regulates several cell functions such as proliferation, apoptosis, survival, migration, and invasion [117,118]. Many signaling pathways that regulate these cellular functions were shown to have c-SRC involvement, namely PI3K/AKT/HIF-1α, RAS/RAF/ERK1/2, FAK/p130CAS/MMP9, STAT3/c-MYC/CYCLIND1, β-CATENIN/c-MYC/CYCLIND1, and RAC/NADPH [119,122,123]. This explains, by targeting c-SRC, miR-205 has potential to target these many downstream pathways to exert its tumor suppressive function.

Exploring the multifaceted targeting ability of miR-205, Hagman with his group [103] reported that ectopic expression of miR-205 directly binds to 3′UTR region of androgen receptor (AR) and reduces its gene and protein production in VCaP, 22Rv1, PC-3, and LNCaP prostate cancer cell lines (Fig. 6). However, LNCaP cells showed a significant decrease only on mRNA transcript levels, but not that prominent on protein levels. A possible underlying reason for this could be other signaling pathways interfering with AR as explained by Lin *et al.* that PI3K–AKT pathway degrades the phosphorylated form of AR [124]. Further, it was also validated that miR-205 inversely targets PSA levels in prostate cancer which is regulated by androgen receptor signaling [103]. This group further performed an AGO2 based RIP-Chip assay to determine other possible signaling that are targeted by miR-205. miR-205 was found to target several genes related to tumor progression such as Early growth response 1 (EGR1), Epithelial cell adhesion molecule (EpCAM), Chemokine (C–C motif) ligand 20 (CCL20), Fibroblast growth factor-binding protein 1 (FGFBP1), Cadherin 1, type 1, E-cadherin (CDH1), FBJ murine osteosarcoma viral oncogene homolog B (FOSB), Jun B proto-oncogene (JUNB), Interleukin 8 (IL-8), Endothelin-1 (EDN1), Transcription factor 3 (ATF3), and few members of the nuclear receptor family Nuclear receptor subfamily 4, group A, member 1, 2, and 3 (NR4A1), (NR4A2), and (NR4A3). Some of these targets were further evaluated *in vitro* by the group as ectopic expression of miR-205 decreased the levels of IL-6 (in LNCaP and 22Rv1 cells) and increased the expression of EpCAM (in LNCaP and PC-3 cells) and E-cadherin (in PC-3 and 22Rv1 cells) [103]. Previously published studies in accordance to Hangman's report also indicated some of the targets for miR-205 determined through RIP-Chip analysis in different cancers such as IL-24 [90], EGR1 and IL-18 [125], PKP3, IL-6, CDH3, EDN1 and FOS [89], and CYR61 [14]. MAPK is another signaling pathway that is targeted by miR-205. MAPK is a known cell survival promoting oncogenic pathway in prostate cancer which regulates phosphorylation of androgen receptor [103].

4.4. Regulation of cell proliferation and growth

Many studies indicated that miR-205 halts cell proliferation and growth in variety of cancers [126–129], including prostate cancer [130,131]. In this direction, Wang *et al.* [116] investigated the role of miR-205 in prostate cancer cell proliferation/growth *in vitro* and *in vivo.* miR-205 was transiently overexpressed in PC-3 and DU-145 prostate cancer cells. Results revealed that in the presence of miR-205, cells showed a significant decrease

in proliferation rate as well as in colony forming ability when compared with negative control. *In vivo* findings were in accordance with cellular results as DU-145 prostate cancer xenograft mouse model corroborated anti-tumor properties of miR-205. In this mouse model, tumor generation was delayed, and tumor growth was also significantly suppressed with the restoration of miR-205 when compared with negative control group tumors (Fig. 7 A). Furthermore, immunohistochemistry was performed on tumor tissue sections for a well-known cell proliferation marker, Ki-67. Similar to previous outcomes, expression level of Ki-67 was notably reduced in miR-205 upregulated group than negative controls (Fig. 7 B).

Majid *et al.* [90] reported the transfection efficiency of miR-205 with respect to time and its effect on cell growth and proliferation. Ectopic expression of miR-205 significantly reduced cell proliferation from 8% to 30% in a time dependent manner from 0 to 72 hours of transfection when compared with untransfected cells and/or cells transfected with non-specific control miR. Similarly, clonogenic potential of these miR-205 transfected cells was also reduced compared to control groups. A cell viability assay for growth kinetics was performed for 3, 5, and 7 days with PC-3 and LNCaP prostate cancer cell lines, ectopically overexpressed with miR-205 [91]. At day 7, cell proliferation/number of cells in both cell lines was significantly reduced in miR-205 transfected cells when compared to negative control transfected group. Two other studies [132,133] have also validated that miR-205 directly targets HMBG3 and centromere protein F, and suppresses their expression which leads to decreased cell proliferation and growth.

4.5. Regulation of invasion, migration, and metastasis

Prostate cancer mostly metastasizes to other vital organs such as lung, liver, and bones. Advanced stage prostate cancer cells can penetrate basement membrane and evade to other organs *via* EMT process, this transition is required for cancer cell metastasis [134,135]. During the EMT process, several molecular changes take place within the cells such as E-cadherin downregulates and thereupon N-cadherin levels elevate after being modulated by Snail, a known EMT transcription factor. This shift in the expression of these cell adhesion molecules denotes prostate cancer metastasis and even reoccurrence after radical prostatectomy [136].

Growing evidence favors miR-205 being a great regulator of EMT. To explore the mechanistic role of miR-205 in prostate cancer metastasis and EMT, Gandellini along with group [27] restored miR-205 in DU-145 and PC-3 prostate cancer cells which resulted in marked morphological changes leading to transition from fibroblastic phenotype to epithelial type phenotype as noticed by an increased number of large polygonal flattened cells, and decreased migration (32±20% and 57±15% in DU-145 and PC-3, respectively) and invasion (71±14% and 53±9% in DU-145 and PC-3, respectively) of these cells than negative control treated cells (migration and invasion abilities were recorded around ~ 90% in both cells). Further, this phenotype transition from mesenchymal to epithelial like characteristics was confirmed at molecular level as indicated by increased expression of E-cadherin and β-catenin (Epithelial markers) and reduced expression of a classic mesenchymal marker, Vimentin in DU-145 and PC-3 cells after 3 days of transfecting with

miR-205. In addition to these EMT/MET markers, several other oncogenes associated with prostate cancer progression such as IL-6, N-chimerin, ERBB3, E2F1, E2F5, PKCε, EZH2 and Caveolin-1 were found to be downregulated in miR-205 transfected cells. Interestingly, ZEB2 expression was significantly inhibited (55.9±7.8% in DU-145 and 44.2±19.1% in PC-3) in miR-205 transfected cells as compared to negative control treated cells. Computational prediction tools suggested ZEB2 as one of the direct targets of miR-205. Moreover, ZEB2 is known to suppress E-cadherin, suggesting that miR-205 drives MET through upregulation of E-cadherin *via* targeting/downregulating ZEB2 [117].

Src Family Kinases (SKFs) are made of several non-receptor tyrosine kinases namely, Src, Lyn, Fyn, Yes, Hck, Blk, Lck, Yrk, and Fgr; out of which Src and Lyn are reported to be overexpressed in prostate cancer cells and tissues [137,138]. However, thus far Src (c-Src) is the widely studied and well characterized member of SFKs [139]. Separate other lines of evidences also suggest that inhibitors of Src resulted in prostate cancer metastasis and growth/progression inhibition in preclinical studies [140,141]. Considering this, a study [116] further confirmed that c-Src is a direct substrate of miR-205. Ectopic expression of miR-205 in prostate cancer cells clearly reduced the luciferase activity of 3'UTR of c-Src. In addition, c-Src and its phosphorylation was also decreased with the restoration of miR-205 in these cells at translational levels which eventually resulted in reduced FAK/ERK1/2 signaling leading to inhibited prostate cancer tumorigenicity/metastasis.

p63 (TAp63 and ΔNp63, two isoforms), a homolog of p53, is another indirect player in the regulation of cell migration/metastasis. p63 is a tumor suppressor and often downregulated in metastatic prostate cancer [142]. Interestingly, Tucci and colleagues explained that transient expression of p63 (both isoforms) in PrCa cells enhanced luciferase promoter activity of miR-205 by directly targeting this microRNA and resulted in higher expression of miR-205. Further, p63 was shown to exert its anti-metastatic characteristics (regulation of EMT) in miR-205 dependent manner as transiently expressed p63 (ΔNp63) with and without miR-205 inhibition modulated ZEB1 expression differently. In the presence of anti-miR-205, ΔNp63 did not affect ZEB1 protein expression, however with scrambled control, there was a marked reduction in ZEB1 protein levels. These findings are suggestive of indirect regulation of EMT by p63 through ZEB1 suppression *via* direct targeting of miR-205 [142].

5. miR-205 as an adjuvant therapeutic agent

miR-205 is an established tumor suppressor in prostate cancer and thus has been investigated for its additive or adjuvant therapeutic potential (Fig. 8). In this section, we will discuss the adjuvant therapy benefits of miR-205 with radiation and different chemotherapies.

5.1. Radiosensitizer

Localized prostate cancers (non-metastatic, accounts for around ~80% of all clinically diagnosed prostate cancers) are often treated with surgery and radiation [143,144]. Radiation has been in use as a sole therapeutic tool for early stage PrCa (small sized difficult to operate tumors) and as an adjuvant to surgery and chemotherapy [145]. However, cancer recurrence rate has been reported to be high for radiation treated patients primarily due to poor

radiosensitivity (occurrence of resistance to radiation) of cancerous cells [146]. Therefore, the role of miR-205 in radiosensitization of various prostate cancer cells was further determined [147]. Ectopic expression of miR-205 sensitized LNCaP and DU-145 PrCa cells to 5 Gy irradiation dose as demonstrated by decreased cell growth/survival (reduced clonogenic potential). It was shown to inhibit radiation-induced autophagy in PrCa. Western blot analysis indicated that miR-205 enhanced the levels of p62 (inhibited degradation) in LNCaP cells after irradiation. This effect was a result of late phase autophagy inhibition as inhibited expression/accumulation of LC3-I and LC3-II was observed in the presence of a late phase autophagy inhibitor (bafilomycin A1). This inhibition of radiation induced autophagy promoted cellular apoptosis with combined 3 MA (an inhibitor of autophagy) treatment as seen by noticeable increased levels of cleaved PARP and cleaved Caspase 3 (hallmarks of apoptosis), in TP53INP1 dependent manner as protein levels of this marker is significantly reduced with miR-205 overexpression.

Another study [148] also demonstrated miR-205 as a radiosensitizer in DU-145 and PC-3 PrCa cells. With reintroduction of miR-205, cells demonstrated an inhibition of colony forming ability in a radiation dose dependent manner (2 – 8 Gy). Authors further developed a xenograft mouse model using miR-205 stable DU-145 cells. This study also proved that miR-205 restoration in DU-145 cells significantly delayed tumor onset and progression with a single dose irradiation of 5 Gy when compared to non-irradiated control mice. The underlying mechanisms of radiosensitization abilities of miR-205 indicated by reduced levels of PKCε, ZEB1, pEGFR, and nuclear pDNA-PK. Moreover, these finding demonstrated that miR-205 hindered these cells' ability to recover from radiation-induced DNA damage. Expression of a DNA-DSBs presence marker called γH2AX foci was delayed with 4 Gy radiation and miR-205 restoration after 4 and 8 hours than compared to negative control transfected cells. Additionally, miR-205 with 4 Gy radiation resulted in higher amount of unpaired DNA as confirmed by longer comet tails representing single cell DNA damage [148].

5.2. Chemosensitizer

Chemotherapy is the first line treatment option for prostate cancer in the clinic, however, its prolonged use is limited due to emergence of drug resistance. An adjuvant to chemotherapy, miR-205 supplementation is needed to discard associated drug resistance phenomenon. Docetaxel is a commonly used chemotherapy. In this context, a study revealed that loss of miR-205 in metastatic prostate cancer cells leads to docetaxel resistance which further results in increased cancer cell growth and transition to mesenchymal phenotype. However, after transfecting docetaxel resistant PC-3 and DU-145 cells with miR-205, an induction in apoptosis was noticed as clearly seen by increased sub G1 population and cleaved PARP expression. Furthermore, miR-205 reestablishment in these docetaxel resistant prostate cancer cells, drastically modulated EMT by upregulating the expression of E-cadherin and downregulating its transcription factors ZEB1 and ZEB2 [149].

Cisplatin is another chemotherapeutic drug that is being used for prostate cancer treatment in the clinical settings but shows drug resistance. Transient expression (ectopically expressed) of miR-205 in prostate cancer cells sensitized cells to cisplatin drug as evident by significant

reduction in cell survival and clonogenic potential, in addition, decreased tumor growth in a xenograft mouse model was also shown. A drastically significant change in IC50 value of cisplatin was observed with miR-205's presence, as in DU-145 cells it dropped from 16.0±2.6 to 4.5±1.5 μM and in PC-3 from 27.7±4.1 to 9.1±1.1 μM. Moreover, restoration of miR-205 reverted EMT and hindered autophagic events which are often seen because of cisplatin resistance in cells. miR-205 overexpression caused a marked shift from EMT to MET as it enhanced E-cadherin and decreased Vimentin [150].

In a separate study, miR-205 delivered by Ultrasound targeted microbubble destruction sensitized prostate cancer cells to cisplatin. Reintroduction of miR-205 in presence of cisplatin decreased prostate cancer cell growth and markedly increased apoptosis when compared to cisplatin alone treatment as confirmed by increased cell population with Annexin V and PI staining, and enhanced expression of important apoptosis related proteins such as Caspase 9 and its cleaved form, and CytoC. miR-205 further enhanced anti-migratory/metastatic properties of cisplatin by increasing the expression of E-cadherin and reducing MMP9 suggesting regulation of EMT. Additionally, inhibition of p-ERK expression was also observed which indicated that miR-205 exerts its chemosensitizing effects on cisplatin leading to growth inhibition and induction of apoptosis through ERK/p-ERK signaling pathway [151].

6. Improved delivery

Viral vectors (adenovirus, retrovirus, and lentivirus) are commonly used to efficiently deliver nucleic acids such as siRNAs, miRNAs, and oligonucleotides into target cells. They can facilitate long-term gene expression in different tissues and organs. Four commonly used viral vectors for the delivery of miRNAs include lentivirus vectors, retroviral vectors, adenovirus vectors, and adeno-associated virus vectors. These viral vectors have unique characteristic features that make some vectors preferable than the others depending on the intended use. However, these viral vectors are associated with several drawbacks mainly high toxicity, poor loading capacity, and immunogenicity which limit their capability to be translated into the clinics [152,153].

Therefore, non-viral delivery tools have been in demand for stably transferring miRNAs to the cells [154,155]. In this context, people have been utilizing nanotechnology-based delivery of such nucleic acid genes [155] (Fig. 9).

Inorganic nanomaterials (gold, iron oxide, mesoporous silicon, quantum dots, and graphene oxide-based nanoparticles) and organic nanomaterials (lipid, polymer, dendrimer, and complex-based nanoparticles) are widely employed as non-viral vectors to deliver miRNAs. The primary criteria of nano-vectors for enhanced miRNA delivery depends on higher encapsulation efficacy, higher water/serum stability, receptor mediated endocytosis, site-specific localization, and uniform tissue distribution. Such concept-based nano-vectors facilitate not only the delivery of higher miRNA amounts but also reduce the required dose of miRNA for improved therapy and minimized systemic side effects [156].

Among several types of nanoparticles that have been used to deliver miRNAs, lipid-based nanoparticles/liposomes have attained huge popularity, however, they experience short half-lives and superior binding to serum plasma proteins [157]. Our team recently utilized a polymer (PEI-PEG) conjugated iron oxide magnetic nanoparticle (MNP) vectors for miR-205 delivery to prostate cancer cells. This novel formulation of PEI-PEG/MNP-miR-205 exhibited an ideal particle size for efficient tumor delivery of ~ 100 nm. PEI-PEG/MNP-miR-205 showed excellent cellular and hemo-compatibility and overcame docetaxel drug resistance in these cells when compared to lipofectamine delivered miR-205. Results clearly demonstrated that after miR-205 was ectopically delivered by PEI-PEG-MNP to prostate cancer cells, cells became more sensitive to docetaxel treatment as evident by reduced cell proliferation and colony formation ability, and activation of apoptosis through increased levels of cleaved PARP and Caspase 3 [158]. Another metal-based formulation (gold particles based/Au nanoparticles) of miR-205 was also reported to stably deliver this miRNA to prostate cancer cells and target/downregulate PKCε by at least 52% and exert anti-tumor functions. Further, restoration of miR-205 through Au nanoparticles in PC-3 prostate cancer cells resulted in 50% cell death even after 5 days of treatment. Moreover, Caspase 3/7 activity was enhanced in these cells after transfecting with Au-miR-205 particles, indicating an induction of apoptosis. In addition, cell migration was clearly inhibited in these cells with miR-205 reintroduction as confirmed by wound healing scratch assay [159]. Herein, nanoparticles-based delivery offers safe and stable delivery of miR-205, ensuring its enhanced therapeutic benefits in prostate cancer.

7. Clinical applications of miR-205 in prostate cancer

This review has detailed various functional roles of miR-205, its importance in diagnosis and screening, and as an adjuvant therapy for prostate cancer. Thus far, PSA test and biopsy are the current tools utilized for PrCa screening and diagnosis. However, PSA detection test often results in inaccurate cancer diagnosis due to its low specificity and biopsy is an invasive method of sample collection which effects patients' quality of life. In this context, miR-205 was found to be a non-invasive detection tool for PrCa with urine samples. As mentioned earlier, miR-205 has reduced expression in metastatic prostate cancer when compared to early-stage cancer and normal prostate epithelium, thus provides cancer specific detection. Moreover, miR-205 expression in urine samples was shown to discriminate between prostate cancer and BPH specimens, which PSA fails to do. Herein, miR-205 has the potential to be used as a non-invasive lead detection biomarker for prostate cancer in clinics. In addition to diagnosis significance, several studies indicated that miR-205 was an excellent adjuvant to chemo- and radio-therapy in PrCa. miR-205 overcomes radio and chemo resistance mainly associated with docetaxel and cisplatin, two key chemotherapeutic drugs for prostate cancer cells, and makes them sensitive toward these therapies. This further opens clinical potential of miR-205 as a novel adjuvant to currently used therapies for PrCa.

7.1. Screening and diagnostic marker

Currently, high levels of PSA is a common marker to not only diagnose prostate cancer but also to see the severity of the disease itself [160–163]. Nevertheless, elevated PSA

levels are often misleading to false cancer prediction as PSA upregulates during several other conditions including infection, inflammation, and benign prostatic hyperplasia, thus, limiting its specificity for prostate cancer diagnosis. On the other hand, PSA screening has significantly advanced the early detection of PrCa but fails to determine prognosis/overall survival/mortality rate of the disease.

The diagnostic potential of miR-205 in prostate cancer was explored by Srivastava and his team [39]. This study utilized 40 PrCa tissues matched with normal adjacent tissues (15 Caucasian American and 25 African American) for differential miRNA expression by qRT-PCR. Findings are suggestive of downregulation of miR-205 (Fig. 10 A), miR-214, miR-221, and miR-99b in PrCa tissues than compared to normal counterparts. These microRNAs were further validated in urine samples obtained from 36 PrCa (18 Caucasian American and 18 African American) patients and 12 normal healthy counterparts (6 Caucasian American and 6 African American) for their potential as non-invasive diagnostic biomarkers. Receiver operating characteristic curves obtained from PCR data indicated that miR-205 (Fig. 10 B) together with miR-214 was significantly downregulated in PrCa urine samples than that of healthy specimens with the ability to discriminate between two groups with 89% sensitivity and 80% specificity.

Identification of miRNAs in urinary samples is relatively a new theory for developing novel non-invasive diagnostic approaches. A more recent study [164] also favors miR-205 to be utilized as non-invasive urinary diagnostic biomarker for PrCa. 23 PrCa urine samples along with 22 benign prostatic hyperplasia and 20 healthy control samples were validated with qPCR for differentially expressed miRNAs. Contradicting to other above-mentioned study, miR-205 was upregulated in PrCa urine samples with no significant difference in BPH and healthy normal control urine samples, however, it was able to discriminate between cancer and BPH groups with 87% specificity over PSA which was reported to have only about 33% specificity [165]. This report is although in contrast regarding miR-205 expression profile in PrCa samples, still advocates for miR-205 to be established as a novel non-invasive diagnostic marker for prostate cancer with higher precision, overcoming the possibility of wrong diagnosis of prostate cancer.

7.2. Prognostic marker

Uncertainty with prognosis of prostate cancer makes it a leading cause of cancer related deaths in men. PSA test is a well-known prognostic factor for prostate cancer. However, low accuracy of this test often leads to false positive/over diagnosis and unnecessary treatment, thus fails to provide adequate prognosis [166–168]. Herein, improved and specific prognostic markers/tools are urgently required to encounter this unmet clinical need for PrCa. miR-205 has been involved in pathogenesis of prostate cancer. Available literature specifies the role of miR-205 in PrCa development, transition to epithelial to mesenchymal phenotypes, aggressive tumor/cell growth and migration/invasion, and overall poor patient outcome [79,169–171] and employs its tumor suppressive role *via* targeting various oncogenic signaling including AR [169], PKCε [27], Bcl-2 [91], and MAPK [28] suggesting its pivotal role in prognosis of PrCa.

Nordby *et al.* [172] after evaluating the downregulation of miR-205 in 14 prostate cancer patients with biochemical failure (PSA ≥ 0.4 ng/mL after surgery) in a screening array of 1435 miRNAs [173], demonstrated its role in the prognosis of prostate cancer in a larger cohort of 535 PrCa patients with prostatectomy patients (localized PrCa) and extensive follow-up. Group reported high miR-205 expression in normal epithelium compared to tumor epithelium using *in situ* hybridization which is significantly related to biochemical failure/relapse having a hazard ratio of 1.64. Clinical failure (relapse of palpable tumor) also exhibited some association with high miR-205 expression in normal epithelium, but it was not significant. However, there was no association found between low miR-205 expression in tumor epithelium and relapse of prostate cancer. These findings are suggestive of prognostic characteristics of miR-205 in the normal epithelium, which seemed to have crosstalk functions with surrounding tissues as well as tumor epithelium.

Another study also presented the synergistic (indirect) prognostic role of miR-205 in PrCa [174]. miR-205 upregulated NKX2–3 which is a key autophagic biomarker in prostate cancer. This group used a multivariate Cox proportional regression model to identify a signature of 6 autophagy-related prognostic genes for prostate cancer. Further, miR-205 was also found as one of the differentially expressed (Decreased expression in PrCa samples than compared to normal samples) miRNAs according to Gene Expression Omnibus database. As per STRING analysis and cBioPortal, NKX2–3 was associated with overall survival of prostate cancer patients and influenced tumor mutation burden and programmed cell death 1 (PDCD1). However, the expression of NKX2–3 was negatively regulated by miR-205, thus suggesting its indirect prognostic (through NKX2-3 regulation) role in PrCa.

8. Summary, limitations, and future directions

Prostate cancer claims thousands of lives every year. Localized prostate cancer is highly curable but due to lack of adequate detection and screening tools, it often leads to misdiagnosis. miRNAs have been the center of recent growing research for the development of novel detection/screening and therapeutic biomarkers. miR-205 is of one such interest that shows great promise in the field of prostate cancer research. miR-205 has exhibited progressive loss in advanced prostate cancer and has been established as an important tumor suppressor which regulates key signaling molecules. Despite showing great promises in preclinical studies, miRNA is far away from being translated into clinics due to its associated stability, targeted organ specific delivery and toxicity issues. Since miR-205 has site/organ specific expression and functional pattern (it can act as both oncogene and tumor suppressor), it becomes of high importance to deliver this miRNA in a controlled and site-specific manner.

In this review, we not only discussed various functional roles of miR-205 but also elaborated feasible mechanistic methods (using nanotechnology) that can be utilized for efficient and safe delivery of this miRNA to fully avail its tumor suppressive and diagnostic potential in humans. However, nanoparticles-based delivery of miR-205 is still an emerging field of research referring to only its physiochemical and *in vitro* investigations and requires future exploration for its theranostic potential *in vivo* and in human applications.

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Data availability

No data was used for the research described in the article.

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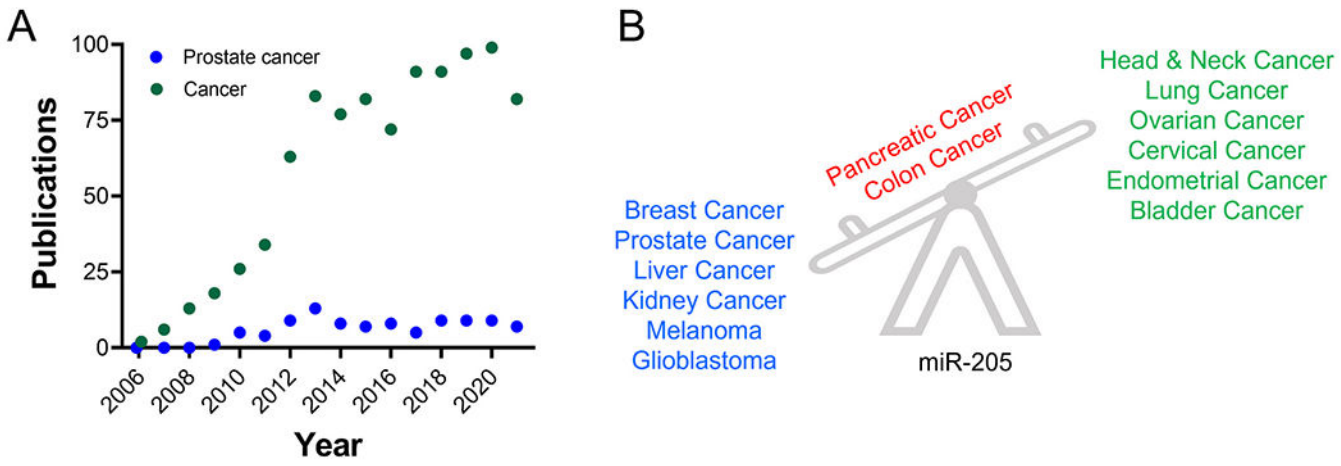

Fig. 1.

Significance of miR-205 in cancer research. A) Graphical representation of number of peer-reviewed articles related to miR-205 with respect to all types of cancers and specific to prostate cancer. The data was retrieved from National Institutes of Health's U.S. National Library of Medicine (Center for Biotechnology Information) under PubMed database search using "miR-205 and cancer" and "miR-205 and prostate cancer" (http://www.ncbi.nlm.nih.gov/pubmed/) over a period of 2006–2021 (search was conducted on March 1, 2022). Each data point represents number of publications in each year. B) Differential expression of miR-205 in different cancers.

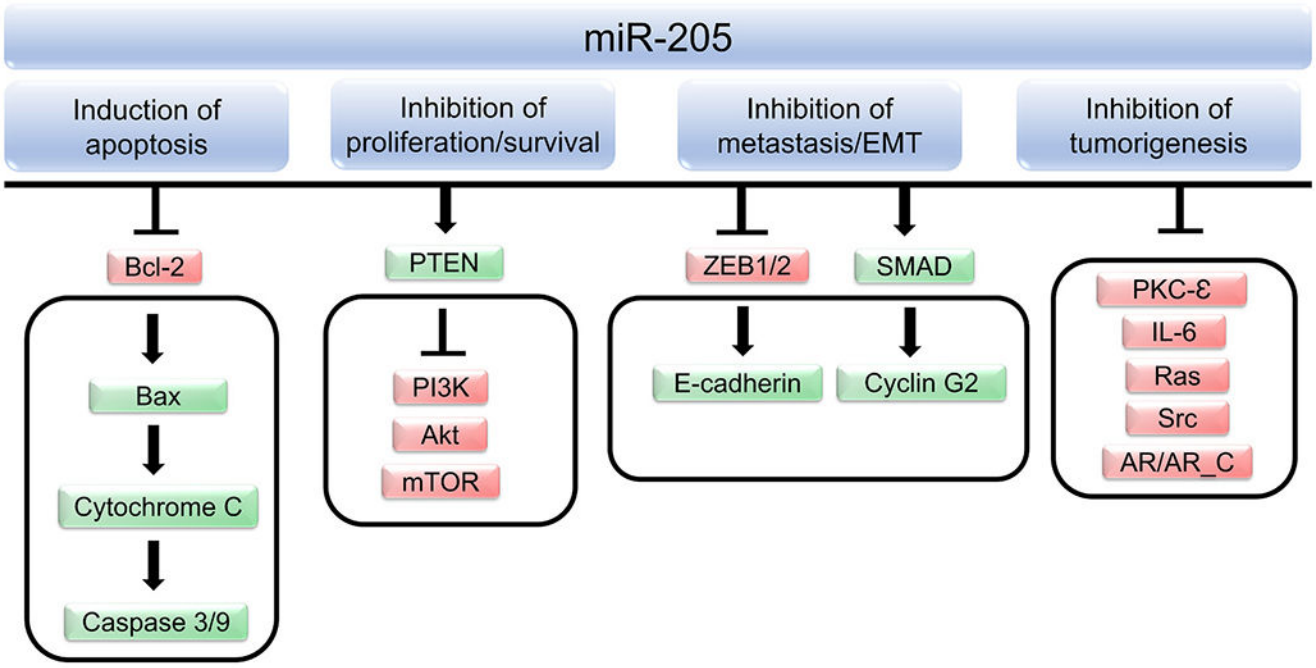

Fig. 2.

Downstream molecular signaling of miR-205 in prostate cancer. miR-205 modulates (activates and/or suppresses) several downstream molecules/pathways to exert its tumor suppressive role *via* mainly regulating apoptosis, proliferation and survival, metastasis and EMT, and tumorigenesis.

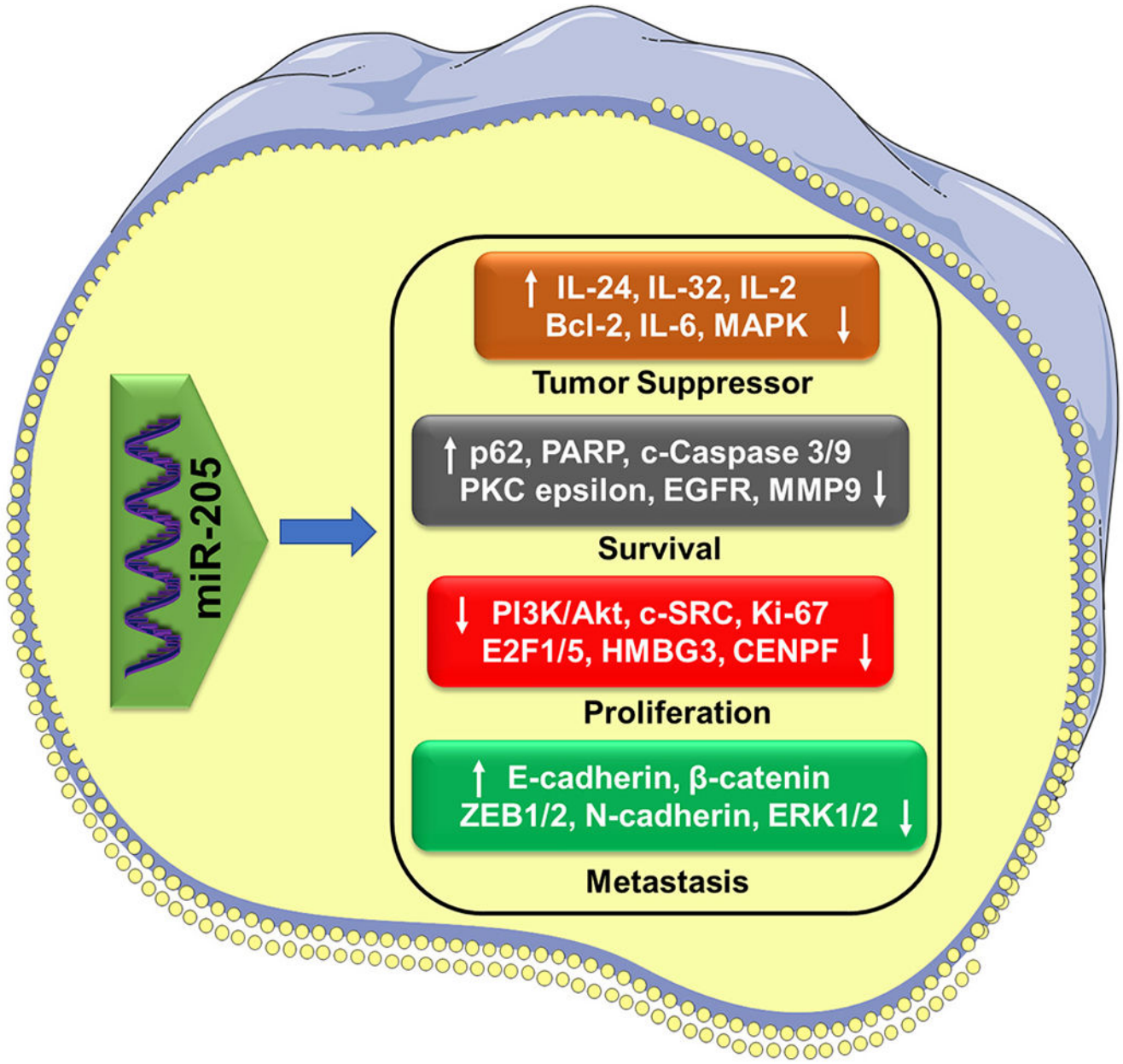

Fig. 3.

Role of miR-205 in various cellular functions in prostate cancer cells. miR-205 is involved in modulating various tumor suppressor, survival, proliferation, and metastasis associated molecules and pathways in prostate cancer cells.

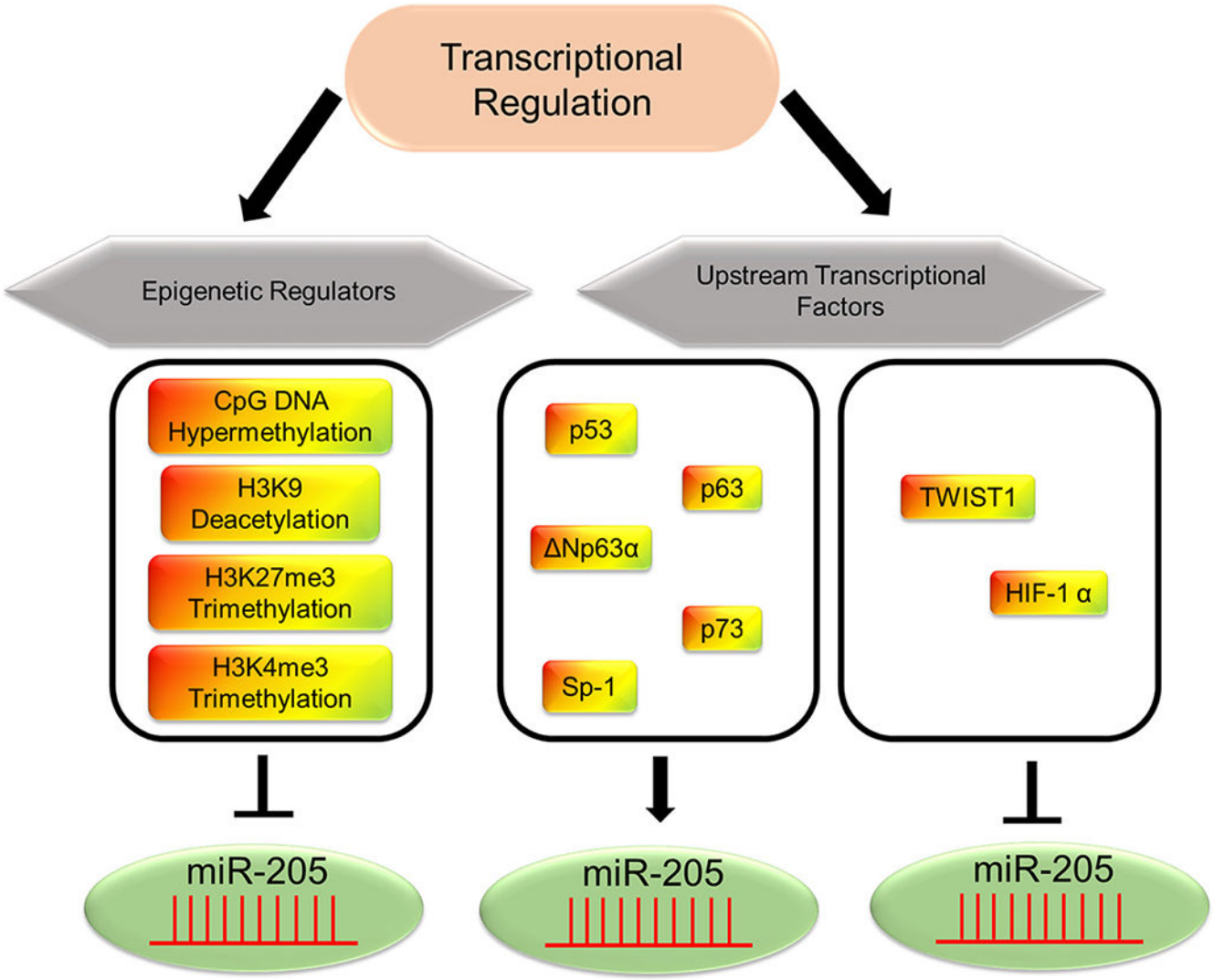

Fig. 4.

Transcriptional regulation of miR-205 in prostate cancer. miR-205 is transcriptionally regulated by epigenetic modulations and *via* several upstream transcriptional factors.

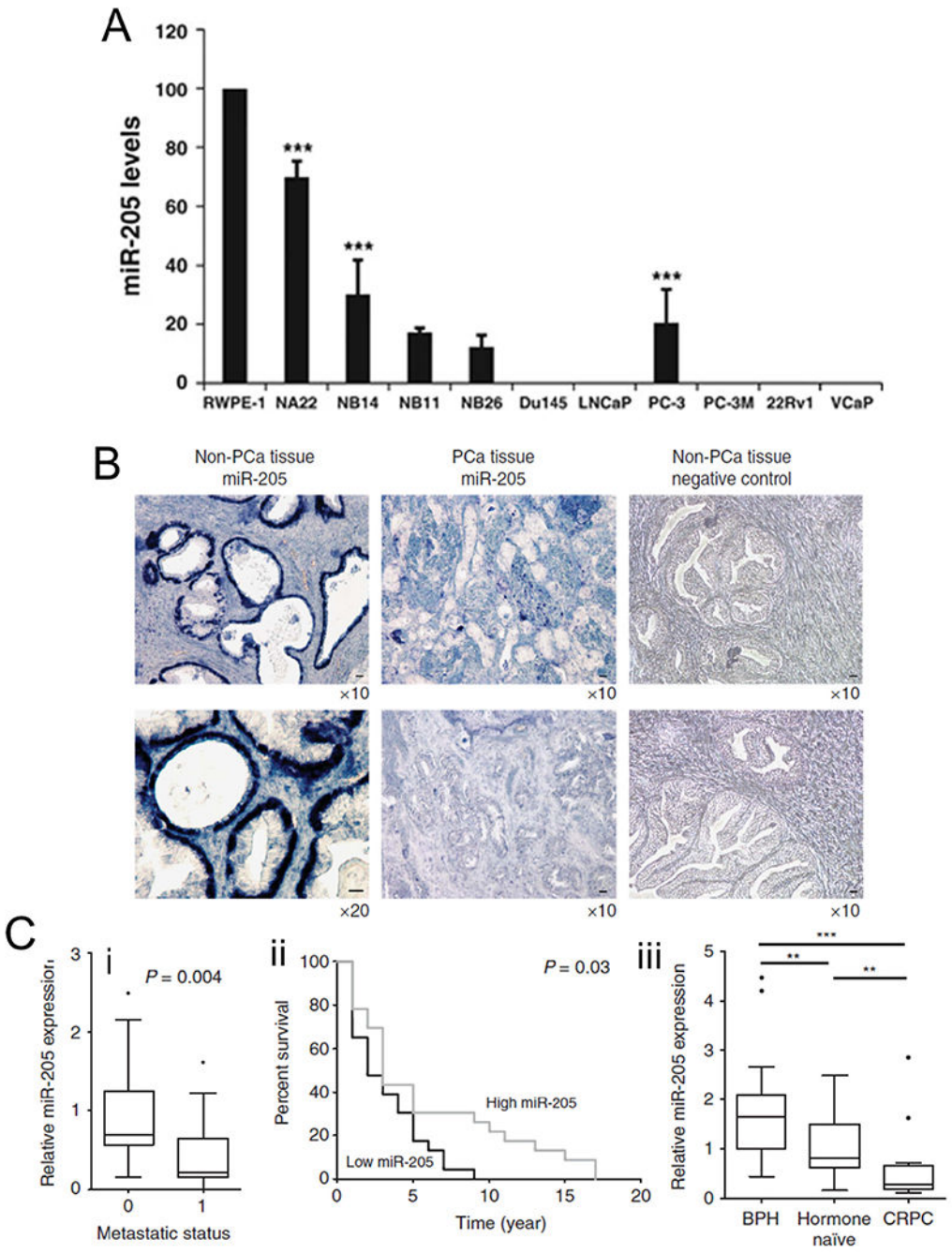

Fig. 5.

miR-205 is significantly downregulated in prostate cancer cell lines and human cancer tissues. A) Real-time PCR analysis of miR-205 in various prostate cancer cell lines and normal prostate epithelial cells. B) *In situ* hybridization of miR-205 in normal human prostate and prostate cancer tissues. C) RT-PCR expression levels of miR-205 in prostate cancer cohort (i) prostate cancer patients with metastasis and without metastases, (ii) patient's Kaplan-Meier survival curves, and (iii) miR-205 levels in benign hyperplasia,

hormone naïve, and castration-resistant prostate cancer tissues. Figures are adopted from references 102 and 103.

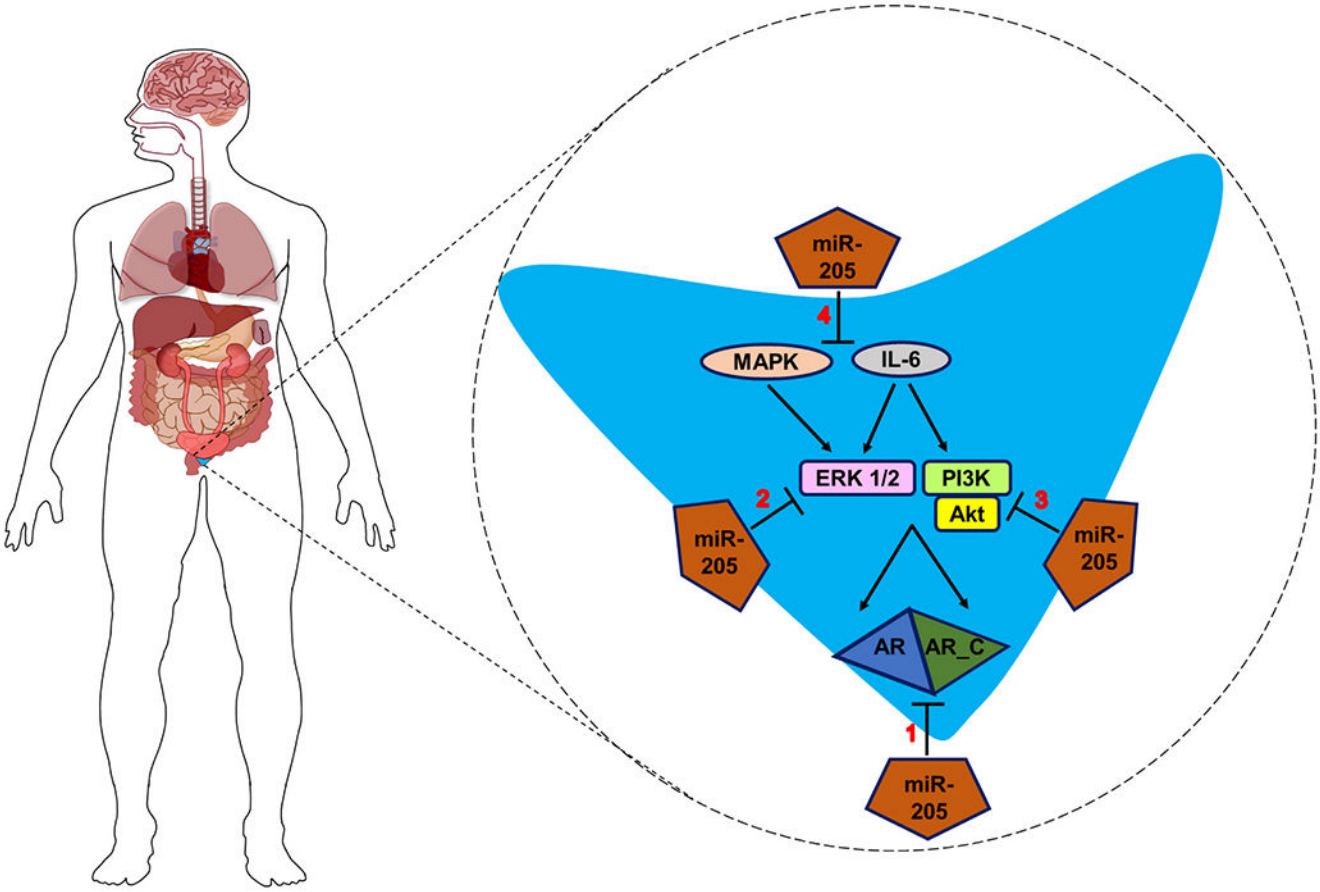

Fig. 6.

Possible multi-channel (1-4) targeting of androgen receptor (AR) and its co-regulators (denoted as AR C in figure) by miR-205 in human prostate cancer.

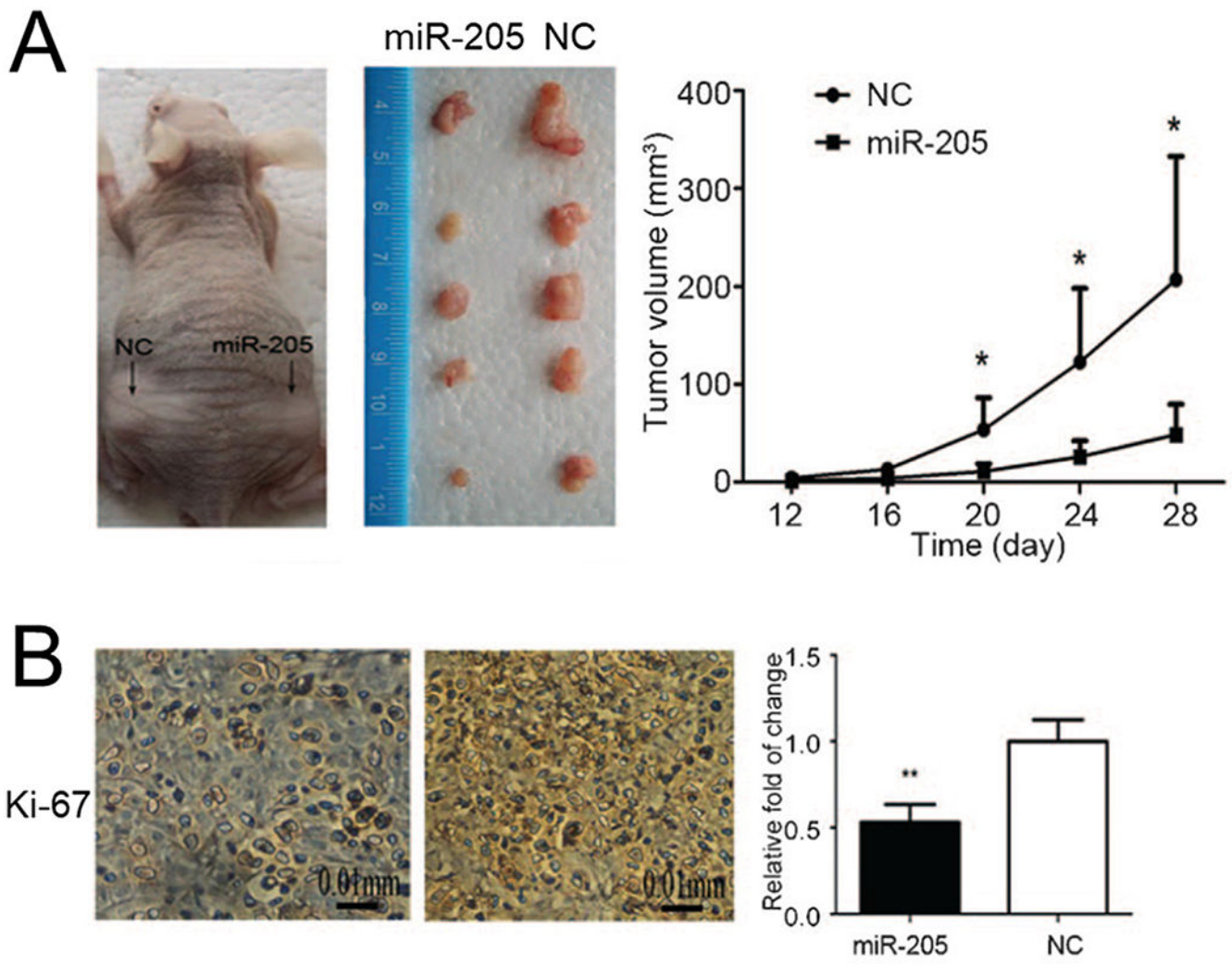

Fig. 7.

miR-205 significantly suppresses tumor growth by reducing proliferating cells in mouse xenograft model. A) The tumor volume of miR-205 group was decreased compared to NC group (image and graphical representation) and B) miR-205 reduced Ki-67 immunostaining in tumor tissues indicating reduction in proliferating cells in tumors. Figure is adopted from reference 116.

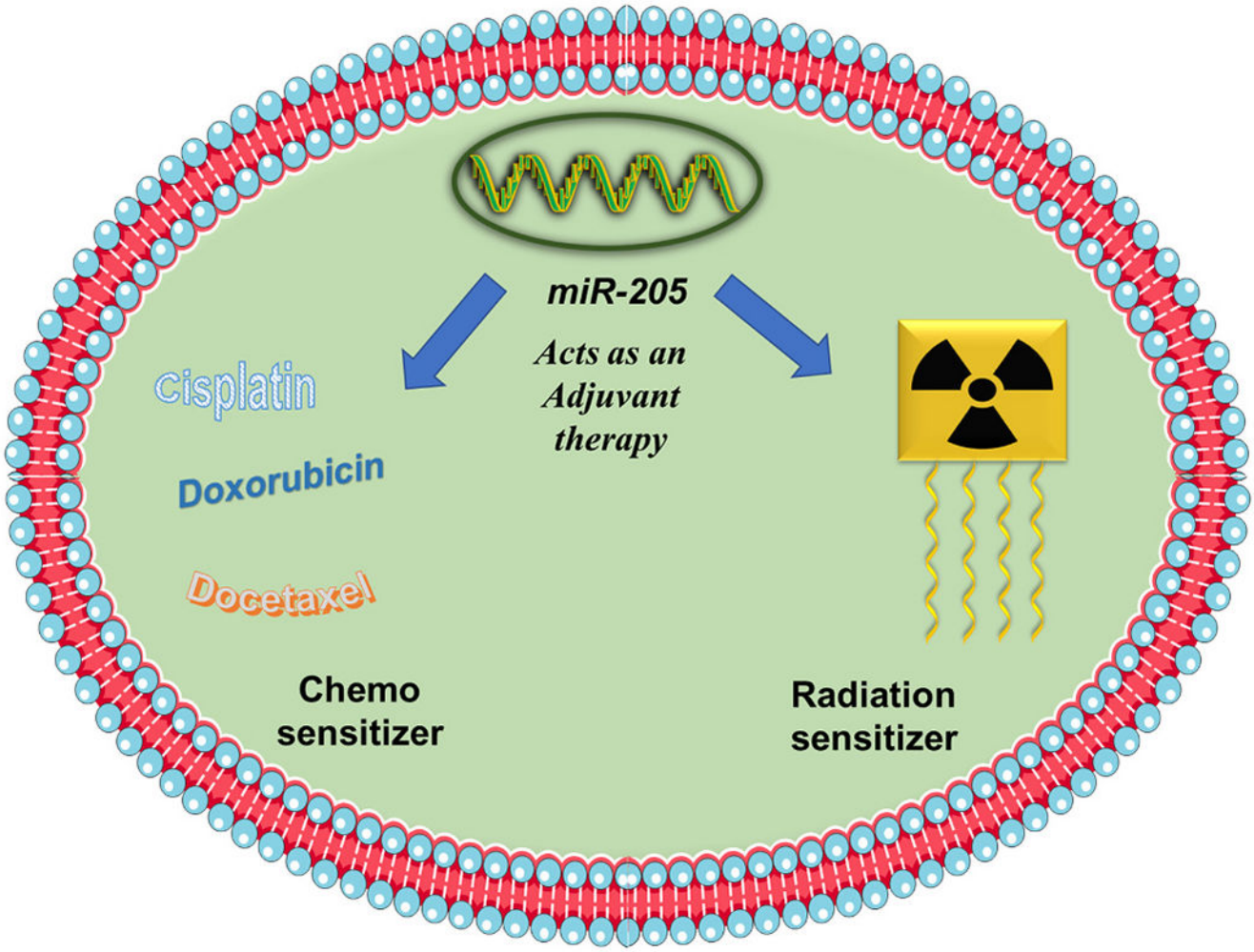

Fig. 8.

miR-205 acts as an adjuvant sensitizing agent for conventional chemotherapeutic drugs and radiation treatment.

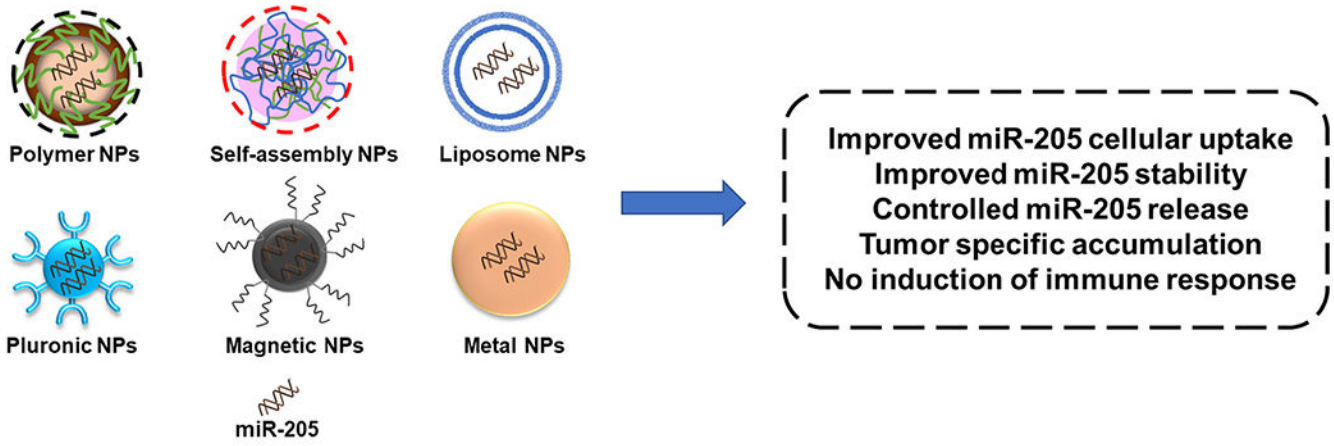

Fig. 9.

Improved delivery of miR-205 through various types of nanoformulations, leading to improved cellular targeting and improved therapeutic benefit.

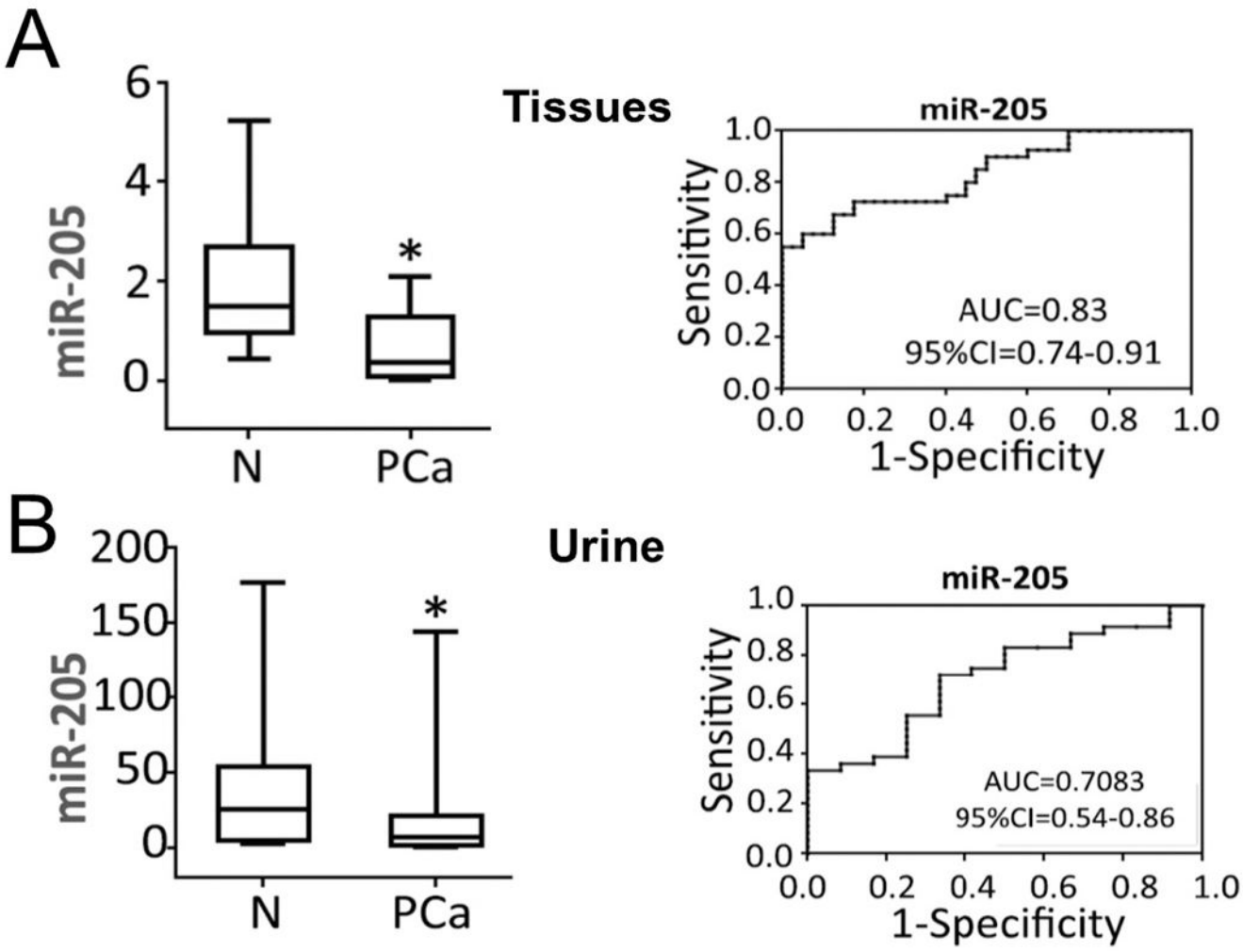

Fig. 10.

miR-205 serves as a potential diagnostic marker. A) Prostate cancer patients exhibited lower amounts of miR-205 in tumor tissues and B) The presence of miR-205 is significantly lower in urine samples of prostate cancer patients. Figure is adopted from reference 39.

Table 1

Published review articles providing details on miR-205 and, its various roles and functions in cancer.

Article, author, and reference	Pertained details
Targeting miR-205 in breast cancer Wu A *et al.* [51]	This review article explores the tumor suppressive role of miR-205 in breast cancer *via* targeting several oncogenes such as ERBB3 and ZEB1.
The ups and downs of miR-205: identifying the roles of miR-205 in mammary gland development and breast cancer Greene SB *et al.* [52]	This review sheds light on the functions of miR-205 in maintaining normal mammary stem cells and developing breast cancer.
MiR-205 in cancer: an angel or a devil? Qin AY *et al.* [53]	In this review, authors describe the epigenetic mechanisms responsible for differential expression and various functions of miR-205.
Insights into the diverse roles of miR-205 in human cancers Orang AV *et al.* [54]	Authors aim at tumor suppressive and oncogenic role of miR-205 in different type of cancers and its involvement in tumorigenesis.
The important roles of miR-205 in normal physiology, cancers and as a potential therapeutic target Vosgha H *et al.* [55]	This group demonstrates the clinical and pathological importance of miR-205 in various cancers depending upon its expression.
MiR-205 dysregulations in breast cancer: The complexity and opportunities Xiao Y *et al.* [56]	This review focuses on the dysregulation of miR-205 in breast cancer and its role in breast cancer cell proliferation, EMT, drug resistance and stemness.
miR-205: A potential biomedicine for cancer therapy Chauhan N *et al.* [57]	Authors summarize the differential role of miR-205 in different cancers and its potential to be a lead biomarker/biomedicine.
Unveiling the ups and downs of miR-205 in physiology and cancer: transcriptional and post-transcriptional mechanisms Ferrari E *et al.* [58]	This review highlights the mechanisms and factors that regulate the expression of miR-205 at transcriptional and post-transcriptional levels.
miR-205 in breast cancer: State of the art Plantamura I *et al.* [59]	This review explains the functional role of miR-205 in breast cancer initiation, progression, tumor microenvironment and stemness.