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Review

Prostate Cancer: De-regulated Circular RNAs With Efficacy in Preclinical *In Vivo* Models

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Abstract

Therapy resistance, including castration-resistance and metastasis, remains a major hurdle in the treatment of prostate cancer. In order to identify novel therapeutic targets and treatment modalities for prostate cancer, we conducted a comprehensive literature search on PubMed to identify de-regulated circular RNAs that influence treatment efficacy in preclinical prostate cancer-related *in vivo* models. Our analysis identified 49 circular RNAs associated with various processes, including treatment resistance, transmembrane and secreted proteins, transcription factors, signaling cascades, human antigen R, nuclear receptor binding, ubiquitination, metabolism, epigenetics and other target categories. The identified targets and circular RNAs can be further scrutinized through target validation approaches. Down-regulated circular RNAs are candidates for reconstitution therapy, while up-regulated RNAs can be inhibited using small interfering RNA (siRNA), antisense oligonucleotides (ASO) or clustered regularly interspaced short palindromic repeats/CRISPR associated (CRISPR-CAS)-related approaches.

Keywords: Circ RNA-protein interaction, castrate-resistant prostate cancer (CRPC), drug delivery, metastasis, miR-sponging, siRNA, review.

Introduction

Prostate cancer is one of the most common malignancies worldwide. In 2023, 288,000 cases were diagnosed in the US, resulting in 34,700 deaths (1).

Localized prostate cancer can be cured, however, disseminated prostate cancer is associated with a poor prognosis. Treatment options include surgery, radiation, chemotherapy, androgen-deprivation therapy, and inhibition of release of gonadotrophin-releasing hormone.

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Patients with breast cancer (*BRCA*) gene mutations benefit from treatment with poly-ADP ribose polymerase (PARP) inhibitors. However, development of therapy resistance such as castration-resistance and metastasis to distant organs hamper current treatment of advanced prostate cancer and are associated with a poor prognosis (2-4). Due to the immune-suppressive micro-environment and low mutational burden, modest therapeutic benefit was noted in only a very small subset of patients after treatment with immune-checkpoint inhibitory antibodies (5, 6). In addition, the therapeutic potential of immune cell recruitment with bispecific antibodies and chimeric antigen receptor (CAR) T-cell therapy requires further optimization to achieve significant clinical benefits (7). Several antibody-drug conjugates (ADCs) and proteolysis targeting chimera (PROTACs) are currently evaluated in patients with prostate cancer (8-10). Despite ongoing clinical studies, there is a significant need to identify novel targets and develop new treatment modalities. Therefore, we conducted a literature search to identify de-regulated circular RNAs (circRNA) and their corresponding targets that exhibit activity in prostate cancer-related preclinical *in vivo* models. We focused on this category of circRNAs, because demonstration of efficacy in preclinical *in vivo* models is an important milestone in cancer drug development.

Circular RNA

Approximately 98% of human RNAs are non-coding, while only 2% encode proteins (11). Non-coding RNA can be categorized into protein synthesis-related RNAs such as ribosomal and transfer RNAs, regulatory RNAs such as linear long non-coding RNA ≥200 nucleotides (nts), small non-coding RNAs such as microRNA (miRs), small nuclear, small nucleolar RNA, and circ RNA (12). The latter subtype was first identified in plant viroids (13), later found in the human delta hepatitis virus (14), and subsequently found in mammalian cells (15). CircRNAs are highly stable and range in size from under 100 nts to over 4 kb (16). In cancer, circRNAs can exert tumor-suppressive as well as oncogenic properties and accordingly can be down- or up-regulated (17). CircRNAs mediate a plethora of functions, both intracellularly and as exosomes. These functions include sponging of miRs, regulation of transcription, splicing, and translation through protein binding and scaffolding, interaction with RNA, and, in some cases, the encoding of proteins (18). CircRNA can be generated by direct back-splicing, intron-driven circularization, exon skipping, and debranching of intron lariats (18). Circularization generates new junctional sequences, which allow specific targeting of circRNAs (18). Up-regulated circRNAs can be inhibited using siRNA, antisense oligonucleotides (ASO), and CRISPR-CAS (19, 20). The function of down-regulated circRNAs can be restored through gene replacement therapy with expression vectors (21). Diagnostic, prognostic, and therapeutic aspects of circRNAs in prostate cancer have been summarized in several reviews (22-24). In this review, we focus on the therapeutic role of circRNAs in prostate cancer with documented efficacy in preclinical prostate cancer-related *in vivo* models.

Circular RNAs Involved in Therapy Resistance

Circ0004087 mediates paclitaxel (PTX) resistance through up-regulation of mitotic checkpoint ser/thr kinase BUB1. Circ0004087 (Figure 1) was aberrantly over-expressed in prostate cancer tissues (25). Knockdown of circ0004087 led to a decrease in PTX resistance in PC3 and DU145 prostate cancer cells *in vitro* and *in vivo* after subcutaneous (SQ) implantation into nude mice (25). Mechanistically, circ0004087 bound to transcription co-activator Staphylococcal nuclease-domain containing protein 1 (SND1), transactivated transcription factor MYB, and induced expression of BUB1 (25). SND1 is a multifaceted protein involved in transcriptional activation, regulation of mRNA stability, alternative splicing, ubiquitination, and can act as an oncogene in certain types of cancer (26, 27). BUB1 is involved in the spindle checkpoint mediating error-free mitosis correction (28). It has been shown that inhibition of BUB1 reduces PTX resistance in prostate cancer cells (29).

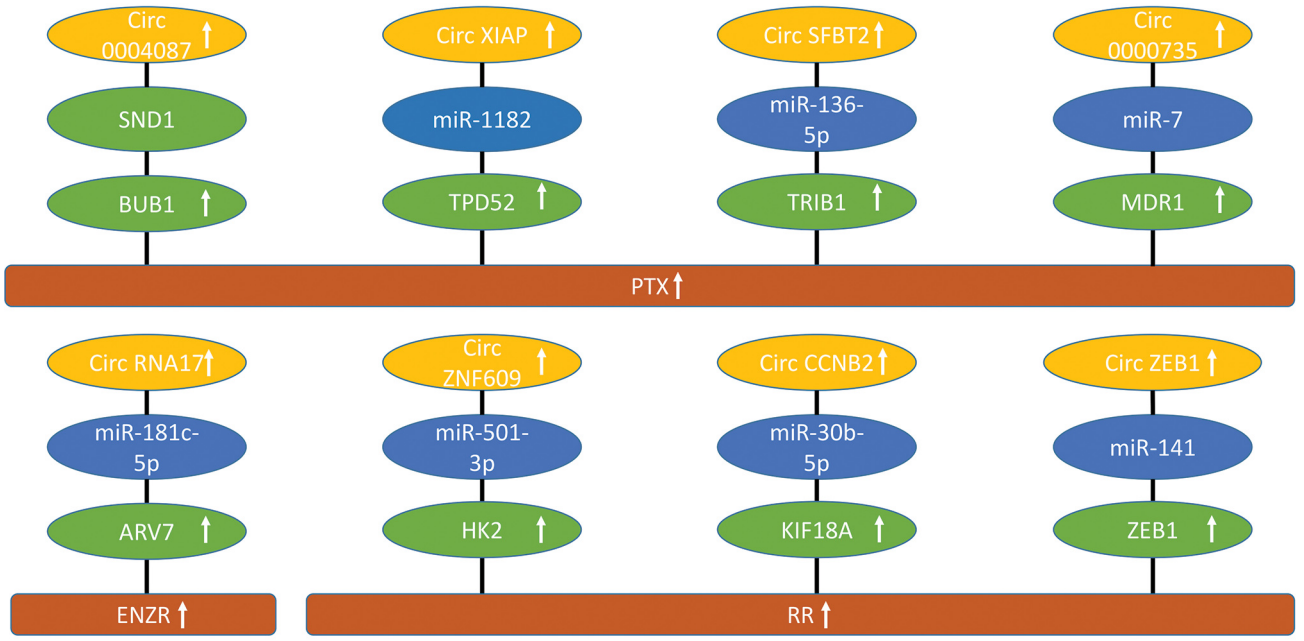

Figure 1. *Circular RNAs contributing to treatment resistance of prostate cancer with efficacy in preclinical in vivo models. First line: specifies circular RNA; second line: indicates type of molecule circRNA is interacting with; third line: highlights de-regulated targets; fourth line: indicates type of resistance. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. ARV7: Androgen receptor splice variant 7; BUB1: mitotic checkpoint ser/thr kinase BUB1; circCCN2: circ cyclin B2; circSFBT2: circ scm-like with four malignant brain tumor domains; circXIAP: circ X-linked inhibitor of apoptosis; circZEB1: circ zinc finger E-box binding homeobox 1; circZNF 609: circ ring finger 609; ENZR: enzalutamide resistance; HK2: hexokinase 2; KIF18A: kinesin family member 18A; MDR1: multi-drug resistance protein 1; miR: micro RNA; PTX: paclitaxel; RR: radio-resistance; SND1: staphylococcal nuclease domain enhancing protein 1; TPD52: tumor protein D52; TRIB1: tribbles homolog 1.*

Circ X-linked inhibitor of apoptosis (circXIAP) mediates PTX-resistance by up-regulating tumor protein D52 (TPD52). CircXIAP (Figure 1) was up-regulated in PTX-resistant prostate cancer tissues and cell lines (30). CircXIAP was found in exosomes and its depletion in PTX-resistant DU145 and PC3 cells increased PTX-sensitivity *in vitro* and in nude mice (30). CircXIAP sponged miR-1182 and up-regulated TPD52 (30). The latter has been shown to be involved in protein trafficking and cytokinesis (31). TPD52 is over-expressed and amplified in prostate cancer and induces prostate cancer cell growth by transactivation of nuclear factor κB (NFκB) (31, 32). Furthermore, TPD52 inhibits apoptosis and promotes metastasis in preclinical prostate cancer-related models (33-35).

Circ scm-like with four malignant brain tumor domains (circSFBT2) induces PTX-resistance by up-regulating tribbles homolog 1 (TRIB1). Exosomal circSFBT2 (Figure 1) increased PTX-resistance in prostate cancer cells *in vitro* and *in vivo* in nude mice. CircSFBT2 sponged miR-136-5p and up-regulated TRIB1 (36). The latter is a member of the SER-THR pseudokinase family, which can act as tumor suppressors as well as tumors promoters (37). The C-terminus of TRIB1 controls stability of interacting proteins through ubiquitination and proteasome-dependent degradation (37). TRIB1 is frequently over-expressed and amplified in prostate cancer and promotes cell survival by regulation of endoplasmic reticulum chaperone expression (38, 39).

Circ0000735 induces PTX-resistance by up-regulating multi-drug resistance protein 1 (MDR1). Circ0000735 (Figure 1) was up-regulated in PTX-resistant prostate cancer tissues and cells (40). Inhibition of circ0000735

increased PTX sensitivity of DU145-PTX and PC3-PTX resistant cells, both *in vitro* and *in vivo* in nude mice. Circ0000735 sponged miR-7 and up-regulated MDR1, cyclin D1, and B cell lymphoma 2 (BCL2), mediators of chemo-resistance, viability, progression, and colony formation of prostate cancer cells (2, 40-43).

Circ RNA17 inhibits enzalutamide resistance (ENZ-R) by down-regulating androgen receptor splice variant 7 (ARV7). CircRNA17 (Figure 1) was down-regulated in prostate cancer tissues and cell lines (44). CircRNA17 inhibited the expression of ARV7 in CRPC C4-2 cells, reduced proliferation and invasion, and increased sensitivity to androgen receptor (AR) antagonist enzalutamide (ENZ) *in vitro* and in an orthotopic nude mice model. This effect also involved miR-181c-5p (44). The underlying mechanism requires further investigation to be fully understood. ARV7 is a C-terminally truncated version of the AR, which lacks hormone binding activity (45). It has been shown that ARV7 contributes to prostate cancer progression, as well as resistance to ENZ and abiraterone (46, 47). It has also been demonstrated that ARV7 causes PTX resistance by inactivation of the spindle assembly checkpoint (48).

Circ zinc finger 609 (circZNF609) induces radio-resistance by up-regulating hexokinase 2 (HK2). CircZNF609 (Figure 1) was highly expressed in prostate cancer tissues and its knockdown in DU145 and VCaP cells decreased viability, migration, invasion, glycolysis, and increased sensitivity against radiation (49). Silencing of circZNF609 elevated radiosensitivity of DU145-related xenografts in nude mice. CircZNF609 sponged miR-501-3p and up-regulated HK2 (49). It has been shown that HK2, the rate-limiting enzyme of glycolysis, mediates radio-resistance in tumors such as cervical cancer, hepatocellular carcinoma (HCC), and laryngeal carcinoma (50-52).

Circ cyclin B2 (circCCNB2) mediates radio-resistance by up-regulating kinesin family member 18A (KIF18A). CircCCNB2 (Figure 1) was found to be up-regulated in radiation-resistant prostate cancer tissues and cell lines (53). Knockdown of circCCNB2 increased radio-sensitivity of prostate cancer cells *in vitro* and in xenografts in nude mice. CircCCNB2 inhibited autophagy of prostate cancer cells by sponging miR-30b-5p and up-regulating KIF18A (54). KIF18A is a member of the kinase family of motor proteins that are associated with microtubules (54). KIF18A is correlated with radio-resistance in esophageal and prostate cancer (55, 56).

Circ zinc finger E-box binding homeobox 1 (circZEB1) mediates radio-resistance by up-regulating transcription factor ZEB1. CircZEB1 (Figure 1) was up-regulated by testicular receptor 4 (TR4), and quaking (QKI). CircZEB1 sponged miR-141-3p, resulting in up-regulation of ZEB1, which mediates radio-resistance of prostate cancer cells (57). TR4 functions as a nuclear receptor in prostate cancer (58). QKI is an RNA binding protein, which is up-regulated by AR in prostate cancer (59). Regarding radio-resistance, it was shown that combination therapy involving radiation therapy and metformin promoted radiosensitivity in preclinical mouse models of prostate cancer (57, 60). ZEB1 has been identified as a promoter of epithelial-mesenchymal transition (EMT) and stem cell properties in prostate cancer (61) and as a mediator of DNA damage response in breast cancer (62).

Circular RNAs Modulating Expression of Transmembrane and Secreted Proteins

Circ homeodomain interacting protein kinase 3 (circHIPK3) up-regulates metadherin (MTDH). CircHIPK3 (Figure 2) was up-regulated in prostate cancer tissues, mediated proliferation, migration, and invasion of PC3 and 22Rv1 prostate cancer cells *in vitro* and promoted growth of corresponding xenografts in nude mice. It also sponged miR-448 and up-regulated MTDH (63). The latter is also known as astrocyte elevated gene 1 (AEG1) and functions as a transmembrane protein in the plasma membrane, endoplasmic reticulum, nucleus, and nucleoli (64, 65). Plasma membrane MTDH was preclinically validated as a

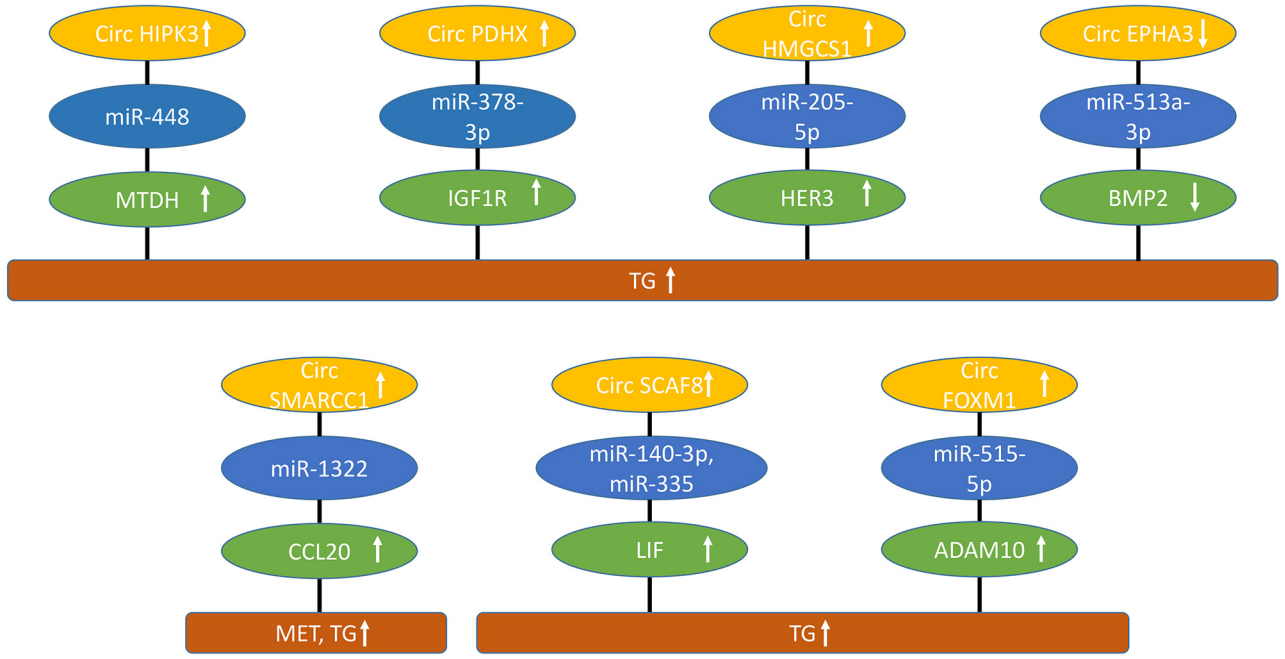

Figure 2. *Circular RNAs targeting prostate cancer-related transmembrane and secreted proteins with efficacy in preclinical in vivo models. First line: specifies circRNA; second line: indicates miRs interacting with corresponding circRNA; third line: highlights de-regulated targets; fourth line: indicates impact on tumor growth and metastasis. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. ADAM10: A disintegrin and metalloproteinase domain containing protein 10; BMP2: bone morphogenetic protein 2; CCL20: C-C chemokine ligand ligand 20; circFOXM1: circ forkhead box M1; circ EPA3: circ EPH receptor A3; circHIPK3: circ homeodomain interacting kinase 3; circHMGCS1: circ hydroxymethylglutaryl-CoA-synthase 1; circ PDHX: circ pyruvate dehydrogenase complex component X; circSCAF8: circ SR-related CTD-associated factor 8; circSMARCC1: circ SWI/SNF related matrix associated, actin dependent regulator of chromatin, subfamily C, member 1; HER3: human epidermal growth factor receptor 3; IGF1R: insulin-like growth factor receptor 1; LIF: leukemia inhibitory factor 8; M: metastasis; miR: micro RNA; MTDH: metadherin; TG: tumor growth.*

target for the treatment of breast cancer metastasis (65) and is currently evaluated as a target in multiple types of cancers (66). In a preclinical prostate cancer *in vivo* model, it has been shown that genetic ablation of MTDH inhibits progression and metastasis (67). Furthermore, it has been demonstrated that inhibition of MTDH enhances the sensitivity of prostate cancer cells to cisplatin (68).

Circ pyruvate-dehydrogenase complex component X (circPDHX) up-regulates insulin-like growth factor 1 receptor (IGF1R). Expression of circPDHX (Figure 2) was associated with poor prognosis in patients with prostate cancer (69). Circ PDHX promoted proliferation and colony formation of 22Rv1 and PC3 prostate cancer cells *in vitro* and its knockdown in PC3 cells inhibited tumor growth in nude mice. CircPDHX sponged miR-378-3p and up-regulated IGF1R (69). The latter has been considered as a target for treatment of many types of cancer (70). In prostate cancer, insulin-like growth factor 1 (IGF-1)/IGF1R interaction has been shown to promote survival and renewal, migration, spread, and resistance to radiation and castration (71, 72). Multiple agents have been developed that inhibit the IGF/IGF1R axis and evaluated in clinical studies including prostate cancer. They were all terminated, because the projected clinical endpoints were not reached and due to the unavailability of predictive biomarkers (72, 73).

Circ hydroxymethylglutaryl-CoA synthase1 (circ HMGCS1) up-regulates human epidermal growth factor receptor 3

(HER3). CircHMGCS1 (Figure 2) was over-expressed in prostate cancer tissues and promoted proliferation of DU145 and PC3 cells *in vitro,* as well as the growth of these cell lines as xenografts in nude mice. CircHMGCS1 sponged miR-205-5p and up-regulated HER3 (74). The latter is an actionable target for the treatment of advanced prostate cancer and is activated by neuregulin 1 (NRG1), which is expressed by tumor-infiltrating monomyelocytic cells (75). Several anti-HER3 drug-conjugates such as U3-1402 and AMT-562 are currently evaluated clinically for the treatment of solid tumors (75, 76). Furthermore, it has been shown that antibody-based inhibition of HER2/HER3 signaling overcomes heregulin-induced resistance to phospho-inosite-3-kinase (PI3K) inhibition in prostate cancer (77).

Circ EPH receptor A3 (circEPHA3) up-regulates bone morphogenetic protein 2 (BMP2). CircEPHA3 (Figure 2) was down-regulated in high-grade prostate cancer tissues and cell lines (78). It prevented proliferation, migration, and invasion of DU145 and PC3 cells *in vitro*. CircEPHA3 suppressed growth of corresponding xenografts after SQ implantation into nude mice as well as experimental metastasis after tail vein injection. It was revealed that circEPHA3 sponged miR-513a-3p, resulting in up-regulation of BMP2 (78). The latter is a member of the transforming growth factor β (TGFβ) superfamily of proteins, which inhibits proliferation and survival, and modulates the tumor microenvironment (TME) by inducing differentiation of macrophages into osteoclasts (79). It has been shown that BMP2 is lost during prostate cancer progression resulting in inhibition of metastasis (80, 81). In PC3 cells, BMP2 is involved in the suppression of SMAD-1 signaling, induction of p21, retinoblastoma (RB) phosphorylation, and an increase in osteoprotogerin (OPG), which inhibits osteoclastogenesis (82).

Circ SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin subfamily C, member 1 (circSMARCC1) up-regulates C-C chemokine ligand 20 (CCL20). CircSMARCC1 (Figure 2) was up-regulated in prostate cancer tissues and correlated with Gleason score and tumor stage (83). It accelerated proliferation, migration and invasion of DU145 and PC3 cells *in vitro*. CircSMARCC1 promoted tumor growth of prostate cancer xenografts as well as experimental metastasis in nude mice. As an underlying mechanism, sponging of miR-1322 and subsequent up-regulation of CCL20 was identified. CircSMARCC1 was associated with colonization of prostate cancer xenografts by M2 macrophages leading to tumor progression (83). The CCL20/C-C chemokine receptor 6 (CCR6) axis has been shown to promote tumor progression by enhancing proliferation and migration of tumor cells, as well as macrophage polarization in the TME (84, 85). In prostate cancer, suppression of the AR induces activation of the CCL20/CCR6 axis (86). CCR6 expression correlates with prostate cancer progression (87).

Circ SR-related CTD associated factor 8 (circSCAF8) up-regulates leukemia inhibitory factor (LIF). CircSCAF8 (Figure 2) was positively correlated with prostate cancer progression and was also found in urine extracellular vesicles (88). It promoted proliferation, migration, and invasion of 22Rv1 and PC3 prostate cancer cells *in vitro*. CircSCAF8 increased the growth of SQ and orthotopic PC3 xenografts in nude mice, as well as experimental metastasis to the lungs in RM1 murine prostate cancer cells. It sponged miRs 140-3p and -335 and up-regulated leukemia inhibitory factor (LIF). Knockdown of circSCAF8 inhibited LIF, signal transducer and activator of transcription 3 (STAT3), matrix metalloproteinases 2 and 9 (MMP2, MMP9), vascular endothelial growth factor A (VEGFA), and cyclin D1 (88). LIF represents a pleiotropic cytokine of the interleukin 6 (IL6) family, which activates oncogenic pathways such as janus kinase (JAK)/STAT3, mitogen-activated protein kinase (MAPK), ser/thr kinase AKT, and mechanistic target of rapamycin (mTOR) through interaction with the LIF receptor (LIFR). The latter signals after association with the transmembrane co-receptor gp130 (89, 90). A monoclonal antibody directed against LIF (MSC1) and a small molecule inhibiting the interaction between LIF and LIFR (EC359) are presently evaluated in clinical studies in several types of cancer (90, 91). It has

been shown in preclinical models that LIF promotes the expression of CXC-ligand 9 (CXCL9) in tumor-associated macrophages and prevents CD8+ T-cell tumor infiltration, thereby impairing anti-programmed cell death protein 1 (anti-PD1) therapy (92). It was demonstrated that LIF mediates CRPC in preclinical models (93). However, LIF signaling remains complex, since in addition to LIF, the LIFR also binds to cardiotrophin 1 (CTF1), ciliary neurotrophic factor (CNTF), and oncostatin M (OSM) (94). The identification of biomarkers indicating response to LIF-based therapy is still pending.

Circ forkhead box M1 (circFOXM1) up-regulates A disintegrin and metalloproteinase domain-containing protein 10 (ADAM10). CircFOXM1 (Figure 2) was up-regulated in prostate cancer tissues and cells (95). It mediates proliferation, cell-cycle progression, migration, and invasion of prostate cancer cells and promotes tumor growth of prostate cancer-related xenografts in nude mice. CircFOXM1 sponged miR-515-5p and up-regulated ADAM10 (95). In the LNCaP prostate cancer *in vivo* model, dihydrotestosterone, IGF1, and epidermal growth factor (EGF) up-regulate ADAM10 (96). In prostate cancer, ADAM10 can act as an oncogenic sheddase, because ADAM10-cleaved ephrin A5 (EPHA5) mediates prostate cancer metastasis (97, 98). Furthermore, it has been shown that nuclear translocation of ADAM10 can act as a transcriptional regulatory factor *via* interaction with the AR and contributes to pathogenesis and progression of prostate cancer (99).

Circular RNAs that Modulate Expression of Transcription Factors

Circ0074032 up-regulates homeobox A1 (HOXA1). Circ0074032 (Figure 3) was up-regulated in prostate cancer and associated with poor prognosis (100). Its down-regulation curbed proliferation, migration, and invasion of prostate cancer cells *in vitro* and inhibited growth of corresponding xenografts in nude mice. Circ0074032 sponged miR-198 and up-regulated HOXA1 (100). HOXA1 is a member of a family of 38 members that contain a DNA binding domain, contribute to all hallmarks of cancer (101), and are also involved in the pathogenesis of prostate cancer (102). HOXA1 has been identified as a breast cancer oncogene (103). Furthermore, it has been shown that HOXA1 enhances cell proliferation and metastasis of prostate cancer cells by promoting extracellular signal-regulated kinases 1/2 (ERK1/2) and AKT signaling (104).

Circ formin 2 (circFMN2) up-regulates LIM-homeobox gene 2 (LHX2). CircFMN2 (Figure 3) was up-regulated in prostate cancer tissues and correlated with advanced tumor stage, as well as lymph node and distant metastasis (105). In DU145, PC3, and VCaP cells, circFMN2 promoted proliferation, migration, and invasion *in vitro* and its knockdown inhibited the growth of VCaP-derived xenografts in nude mice. CircFMN2 sponged miR-1238 and up-regulated LHX2 (105). LHX2 is a member of the LIM homeobox transcription factor family, which consists of 12 members. Each member contains two LIM-domains and a centrally located homeodomain that interacts with DNA (106-108). In a transgenic breast cancer model, it has been shown that LHX2 induces autocrine and paracrine platelet-derived growth factor receptor (PDGFR) signaling (109). In prostate cancer, the mechanistic role of LHX2 remains to be elucidated in further detail.

Circ dehydrogenase/reductase 3 (circ DHRS3) up-regulates Meis homeobox 2 (MEIS 2). CircDHRS3 (Figure 3) was down-regulated in high-grade prostate cancer (110). It decreased proliferation and migration of DU145 and PC3 cells *in vitro*. Over-expression of circDHRS3 inhibited growth of corresponding xenografts after SQ implantation into nude mice, as well as bone- or lung metastases after intratibial or tail vein injection. CircDHRS3 sponged miR-421 and up-regulated the homeobox gene MEIS2, which acts as a transcription factor (110). Depending on the tumor type, MEIS2 can function as an oncogene or a tumor suppressor (111, 112). In prostate cancer, MEIS2 suppresses proliferation and its decreased expression correlates with poor prognosis (113). Epigenetic silencing

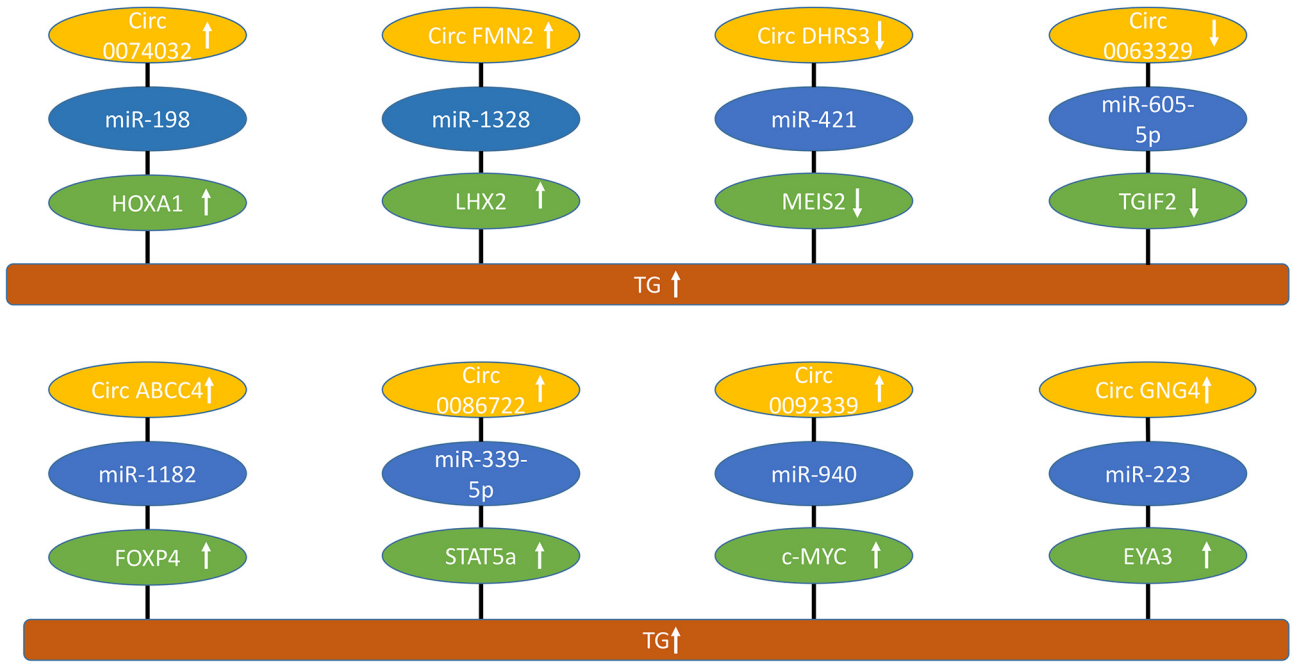

Figure 3. *Circular RNAs targeting prostate cancer-related transcription factors with efficacy in preclinical in vivo models. First line: specifies circRNA; second line: indicates miR interacting with corresponding circRNA; third line: highlights de-regulated targets; fourth line: indicates impact on tumor growth and metastasis. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. c-MYC: Transcription factor c-MYC; circABCC4: circ ATP-binding cassette subfamily C, member 4; circDHRS3: circ dehydrogenase/reductase 3; circFMN2: circ formin 2; circGNG4: circ G-protein subunit gamma 4; EYA3: EYA transcriptional co-activator and phosphatase 3; FOXP4: forkhead box P4; HOXA1: homeobox A1; MEIS2: meis homeobox 2; miR: micro RNA; STAT5a: signal transducer and activator of transcription 5a; TGIF2: TG interacting factor 2; TG: tumor growth.*

of MEIS2 has been observed in patients with prostate cancer recurrence (114).

Circ0063329 up-regulates TG interacting factor 2 (TGIF2). Circ 0063329 (Figure 3) was down-regulated in prostate cancer and inhibited proliferation and migration of DU145 and PC3 cells (115). It decreased growth of SQ implanted PC3 cells in nude mice. Circ0063329 sponged miR-605-5p and up-regulated TGIF2 (115). TGIFs belong to the family of TALE homeoproteins, which act as transcription factors (116). The latter can recruit histone deacetylase 1 after interaction with SMAD4 and act as a co-repressor of SMAD/TGFβ signaling (117, 118). It has been shown that TGIF2 inhibits EMT in prostate cancer (119).

Circ ATP-binding cassette sub-family C member 4 (circABCC4) up-regulates transcription factor forkhead box P4 (FOXP4). The expression of circABCC4 (Figure 3) correlated with a shorter five-year survival rate in prostate cancer patients (120). Inhibition of circABCC4 mediated reduced proliferation, migration, and invasion in DU145 and PC3 cells and decreased tumor growth of corresponding xenografts in nude mice. CircABCC4 sponged miR-1182 and up-regulated transcription factor FOXP4 (120). Forkhead proteins are categorized into subfamilies such as FOXA, FOXC, FOXM1, FOXO, and FOXP and are known to activate or repress genes by recruiting co-factors or repressors. They are commonly de-regulated in cancers (121, 122). They primarily recruit histone deacetylases (121, 122). FOXPs can act as oncogenes as well as tumor suppressors (123). FOXP2 was shown to activate MET receptor tyrosine kinase signaling in prostate cancer (124). FOXP4 was associated with prostate cancer risk in Chinese men (125).

Circ0086722 up-regulates signal transducer and activator of transcription 5a (STAT5a). Circ0086722 (Figure 3) was highly expressed in prostate cancer tissues and cell lines and correlated with worse recurrence-free survival (126). Circ 0086722 promoted prostate cancer cell proliferation and progression *in vitro* and *in vivo*. Circ0086722 sponged miR-339-5p and up-regulated STAT5a (126). Seven STAT proteins have been identified, and they act as transcription factors in response to extracellular signals (127). STATs contain a src-homology 2 (SH2) domain, a DNA binding domain, and a C-terminal transcriptional activation domain (127). STAT5a is a target in prostate cancer and promotes prostate cancer growth *in vitro* and *in vivo* (128, 129). Furthermore, it was shown that STAT5a undergoes amplification during prostate cancer progression (130). Activation of STAT5A predicts early recurrence of prostate cancer in patients treated with radical prostatectomy (131, 132).

Circ0092339 up-regulates transcription factor c-MYC. Circ0092339 (Figure 3) was highly expressed in castration-resistant prostate cancer (CRPC) cells (133). It promoted proliferation of CRPC cells *in vitro* and in nude mice by sponging miR-940 and up-regulating c-MYC (133). c-MYC functions as a pleiotropic transcription factor, which affects proliferation, growth, cell differentiation, metabolism, and apoptosis (134, 135). In prostate cancer, up-regulation of c-MYC is associated with reduced overall survival, lymph node metastasis, and resistance to chemo- and radiotherapy (136). Small molecule c-MYC inhibitor OmoMYC is presently evaluated in cancer patients in clinical trials (137).

Circ G-protein subunit gamma 4 (circGNG4) up-regulates EYA transcriptional co-activator and phosphatase 3 (EYA3). CircGNG4 (Figure 3) was highly increased in prostate cancer (138). It promoted growth of LNCaP and PC3 prostate cancer cells *in vitro,* as well as the growth of PC3 xenografts in nude mice. CircGNG4 sponged miR-223 and up-regulated EYA3 (138). Four eyeless absent proteins (EYAs) have been identified. They associate with sine oculis homeobox (SIX) transcription factors, are translocated into the nucleus, and act as transcriptional co-activators (139). EYAs exhibit tyrosine and threonine phosphatase activity located on separate domains and activate transcription of c-MYC (138, 139). In a breast cancer xenograft model, it has been shown that EYA3 partners with protein phosphatase 2A (PP2A) to induce c-MYC stabilization and metastasis (140). Furthermore, it has been demonstrated that src-phosphorylated EYA3 is a driver of cell proliferation (141).

Circular RNAs Modulating Components of Signaling Pathways

Circ0003258 up-regulates RHO guanine nucleotide exchange factor factor 5 (ARHGEF5) and insulin-like growth factor 2 mRNA binding protein 3 (IGF2BP3). Up-regulation of circ0003258 (Figure 4) was associated with tumor/node/metastases (TNM) stage and tumor grade in prostate cancer patients (142). Circ003258 stimulated EMT in wound-healing and transwell migration assays in DU145 and PC3 cells and metastasis of DU145 cells after tail vein injection in nude mice. Circ 0003258 sponged miR-653-5p, resulting in up-regulation of ARHGEF5. Furthermore, circ0003258 interacted with IGF2BP3 to stabilize histone deacetylase 4 (HDAC4) mRNA. It has been shown that circ0003258 activated ERK signaling in prostate cancer cells (142). ARHGEF5 is a member of the RHO GTPase activating protein (RHOGAP) family and regulates small GTPase RHOA activity (143). IGF2BP3 functions as an RNA binding protein, which can stabilize selected mRNAs (144, 145). HDAC4 is one of 18 different HDACs that remove acetyl groups from histone and other non-histone proteins and which are de-regulated in prostate cancer (146, 147).

Circ midline 1 (circMID1) up-regulates YTH domain-containing protein 2 (YTHDC2). CircMID1 (Figure 4) was up-regulated in prostate cancer tissues and cell lines (148). Its down-regulation inhibited proliferation, migration, invasion, and glycolysis of DU145 and PC3 cells *in vitro* and the growth of SQ implanted PC3 cells in nude mice. CircMID1 sponged miR-330-3p and up-

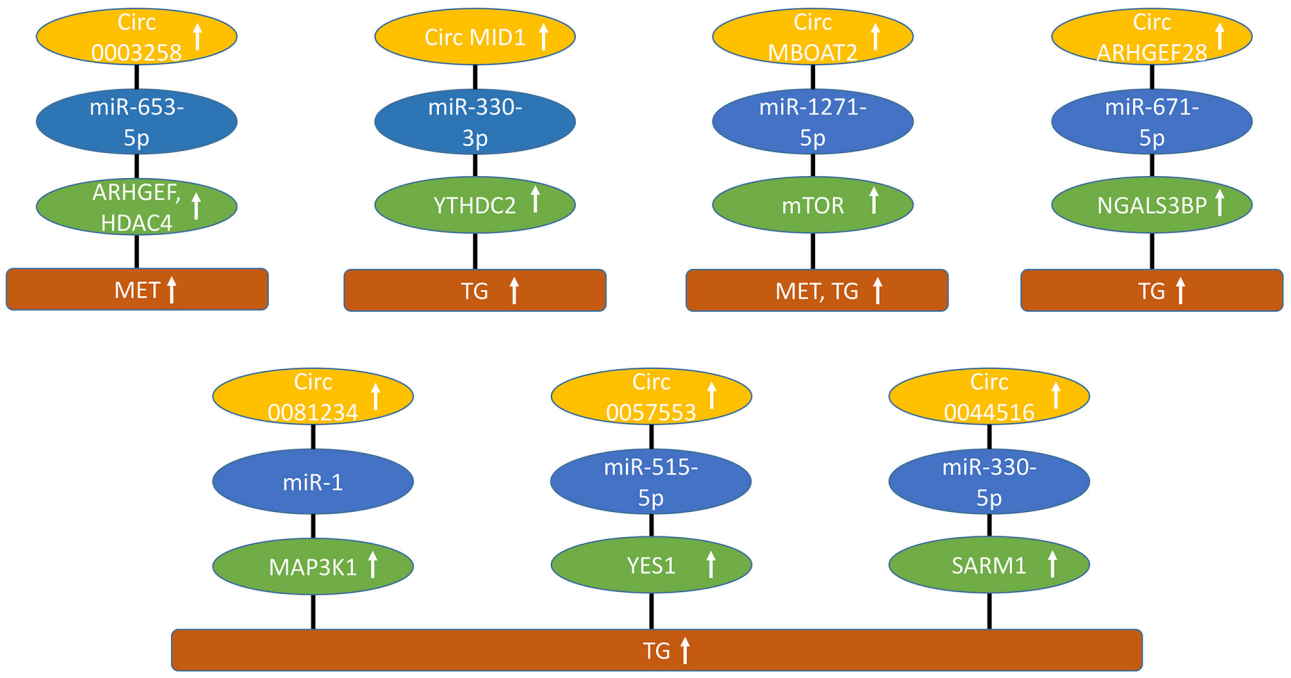

Figure 4. *Circular RNAs targeting prostate cancer-related signaling components with efficacy in preclinical in vivo models. First line: specifies circRNA; second line: indicates miR interacting with corresponding circRNA; third line: high-lights de-regulated targets; fourth line: indicates impact on tumor growth and metastasis. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. ARGEF5: RHO guanine nucleotide exchange factor 5; circARGEF28: circ RHO guanine nucleotide exchange factor 28; circ MBOAT2: circ membrane bound O-acetyltransferase domain containing 2; circMID1: circ midline 1; IGF2BP3: insulin-like growth factor 2 mRNA binding protein 3; MAP3K1: mitogen-activated protein kinase kinase kinase 1; MET: metastasis; miR: microRNA; mTOR: mechanistic target of rapamycin; NGALS3BP: galectin-3- binding protein; SARM1: sterile α and TIR motif-containing 1; TG: tumor growth; YES1: Yamaguchi sarcoma virus 1; YTHD2: YTH domain-containing protein 2.*

regulated YTHDC2. YTHDC2stabilized m6A-modified IGF1R mRNA and induced AKT signaling (148). YTHDC2 functions as a m6A reader (149). It has been shown that YTHDC2 promotes growth, migration, and invasion of prostate cancer cells and its expression predicts poor outcome in prostate cancer patients (150). Furthermore, it was demonstrated that m6A RNA regulators contribute to the progression of prostate cancer (151).

Circ membrane bound O-acyltransferase domain containing 2 (circMBOAT2) up-regulates mechanistic target of rapamycin (mTOR). CircMBOAT2 (Figure 4) was associated with poor prognosis and progression of prostate cancer (152). It promoted proliferation and invasion of DU145 and PC3 prostate cancer cells *in vitro* as well as tumor growth and experimental metastasis of PC3-derived xenografts in nude mice. CircMBOAT2 sponged miR-1271-5p and up-regulated mTOR, resulting in activation of PI3K/AKT signaling (152). The PI3K-AKT-mTOR pathway plays a role in the pro-survival resistance-mediating signaling of prostate cancer and co-operates with AR, MAPK, and wingless/integrated (WNT) signaling pathways (153-155).

CircRHO guanine nucleotide exchange factor 28 (circARHGEF28) up-regulates galectin-3-binding protein (NGALS3BP). CircARHGEF28 (Figure 4) was down-regulated in prostate cancer tissues and cell lines (156). It inhibited proliferation, invasion, and migration of DU145 and PC3 prostate cancer cells *in vitro* and the growth of PC3 and 22Rv1 cells after SQ implantation in nude mice. CircARHGEF28 sponged miR-671-5p and up-regulated

NGALS3BP, inhibiting NFκB signaling (156). NGALS3BP is a secreted, multifaceted protein composed of four domains, with seven potential N-linked glycosylation sites and three O-glycosylation sites. It inhibits activation mitogen-activated protein kinase kinase kinase 7 (MAP3K7), a negative regulator of NFκB signaling (157, 158). It has been shown that NGALS3BP can bind to cluster of differentiation 33 (CD33)-related sialic acid-binding immunoglobulin-type of lectins (SIGLECs) to inhibit neutrophil activation (159).

Circ0081234 up-regulates mitogen-activated protein kinase kinase kinase 1 (MAP3K1). Circ0081234 (Figure 4) was found to be increased in spinal metastases compared to primary prostate cancer tissues (160). It promoted migration, invasion, and EMT in prostate cancer cells and its depletion inhibited the growth of prostate cancer xenografts *in vivo*. It was identified in exosomes and sponged miR-1, leading to up-regulation of MAP3K1 (160). MAP3K1 is a member of a family of 19 MAP3Ks and contains a kinase domain and a plant homeodomain motif, which functions as a ubiquitin-ligase (161). MAP3K1 is involved in the activation of prosurvival MAPKs (162). In prostate cancer, MAP3K1 activates AR-dependent transcription and survival (163).

Circ0057553 up-regulates proto-oncogene homolog of Yamaguchi sarcoma virus 1 (YES1). Circ 0057553 (Figure 4) was found to be up-regulated in prostate cancer tissues and cell lines (164). It promoted viability, migration, invasion, and glycolysis of DU145 and LNCaP cells *in vitro* and tumor growth of LNCaP cells SQ implanted into nude mice. It sponged miR-515-5p and up-regulated YES1 (164). YES1 belongs to the src family of tyrosine kinases, which control signaling pathways, cell proliferation, survival, invasiveness, and are amplified in several types of cancer (165). Several YES1 inhibitors are in clinical trials in cancer patients (165). It has been shown that YES1 mediates invasion and migration of prostate cancer cells (166) and increases their metastatic potential by phosphorylation of focal adhesion kinase (167). YES1 can also mediate PTX resistance in prostate cancer cells (168).

Circ0044516 up-regulates sterile α and TIR motif containing 1 (SARM1). Circ0044516 (Figure 4) was up-regulated in prostate cancer tissues and cell lines (169). Its knockdown suppressed proliferation, migration, invasion of prostate cancer cells and inhibited growth of prostate cancer xenografts in nude mice. It sponged miR-330-5p with subsequent up-regulation of SARM1 (169). SARM1 has been identified as a multifunctional NADPase, which can function as an adaptor protein of toll-like receptors (TLRs), is highly expressed in neurons, and can induce axon degeneration and signaling (170, 171). In prostate cancer, SARM1 promotes proliferation, progression, and metastasis (172). The mechanistic underpinnings of these observations remain to be resolved.

Circular RNAs Modulating Expression of Human Antigen R (huR)

Circ formin 2 (circFMN2) interacts with huR and represses kruppel-like factor 2 (KLF2). CircFMN2 (Figure 5) was up-regulated in prostate cancer tissues and tumor-derived extracellular vesicles and induced proliferation, invasion, and migration of prostate cancer cells (173). Extracellular vesicles from prostate cancer cells also accelerated tumor growth and metastasis of prostate cancer cells in nude mice. CircFMN2 interacted with huR (174), resulting in reduced interaction with KLF2 (173, 175) and reduced KLF2 expression. Also, binding of KLF2 to the promoter of E3-ubiquitinating enzyme RNF128 was decreased, leading to its attenuated expression. It has been shown that down-regulation of RNF128 activates β-catenin/WNT signaling (176). KLF2 also inhibits the migration of prostate cancer cells by down-regulation of MMP2 (177). HuR represents a multifunctional RNA binding protein, which targets mRNAs coding for oncogenes, cytokines, growth factors, and metastasis-promoting factors (174).

Circ exocyst complex component 6B (Circ EXOC6B) up-regulates A kinase anchoring protein 12 (AKAP12) with

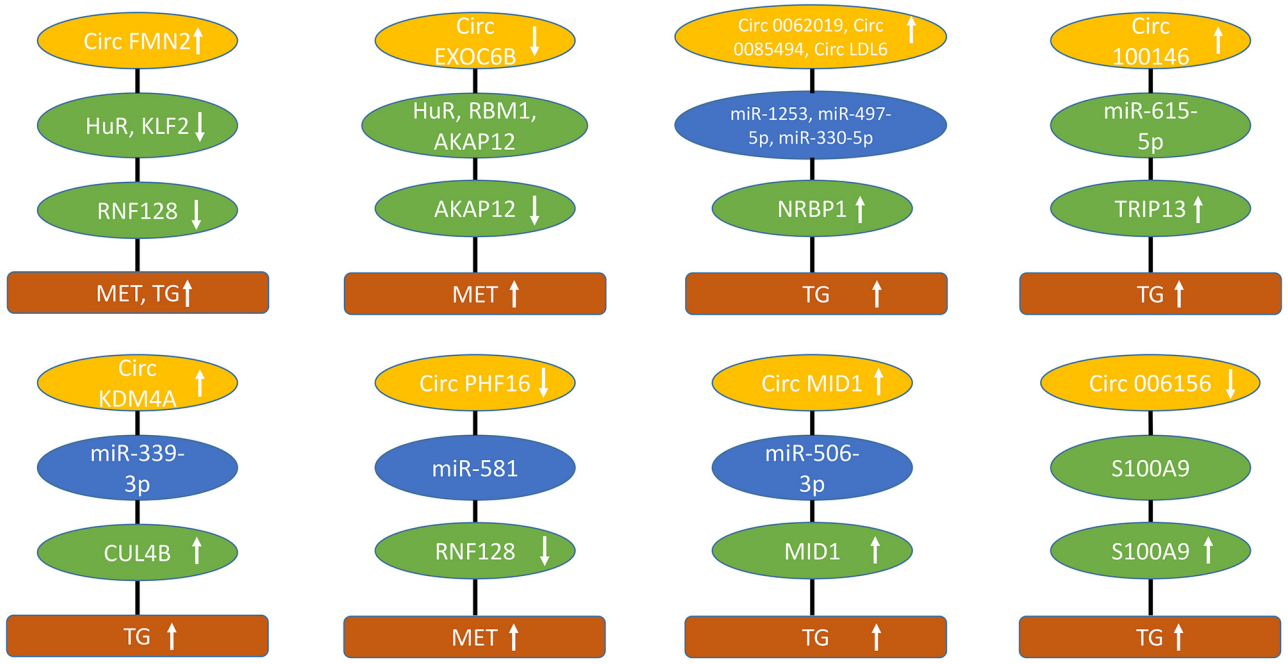

Figure 5. *Circular RNAs targeting prostate cancer-related human R protein, nuclear receptor binding proteins, and ubiquitination pathway components with efficacy in preclinical in vivo models. First line: specifies circRNA; second line: indicates miRs or proteins interacting with corresponding circRNA; third line: highlights de-regulated targets; fourth line: indicates impact on tumor growth and metastasis. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. AKAP12: A kinase anchoring protein 12; circEXO6B: circ exocyst complex component 6B; circFMN2: circ formin 2; circMID1: circ midline 1; circKDM4A: circ RNA lysine demethylase 4A; circPHF16: circ plant homeodomain finger protein 16; circLDL6: circ LDL receptor related protein 6; cul4B: cullin 4B; huR: human antigen R; KLF2: krüppel-like factor 2; MET: metastasis; miR: micro RNA; NRBP1: nuclear receptor binding protein 1; RNF128: ring finger protein 128; S100A9: S100 protein A9; TG: tumor growth; TRIP13: thyroid hormone receptor interacting protein 13.*

the involvement of human antigen R (huR). Low circ EXOC6B (Figure 5) expression correlated with poor prognosis in prostate cancer patients compared to those with high EXOC6B expression (178). CircEXOC6B was down-regulated in prostate cancer tissues and inhibited migration and invasion of DU145 and PC3 cells. In nude mice, circEXOC6B decreased metastasis of DU145 cells after tail vein injection. Circ EXOC6B formed a ternary complex with RNA binding motif single-strand interacting protein (RBM1) (179) and AKAP12, resulting in destabilization of its mRNA (178). AKAP12 acts as a tumor suppressor gene, which can bind to protein kinase A (PKA) regulatory subunits, protein kinase C (PKC), and cytoskeletal elements, such as F-actin stress fibers, and inhibit metastasis (180-182).

Circular RNAs Affecting the Binding of Ligands to Nuclear Receptors

Circ0062019, circ0085494, and circ LDL receptor related protein 6 (circLDL6) up-regulate nuclear-receptor binding protein 1 (NRBP1). Circ0062019, circ0085494, and circLDL6 (Figure 5) were found to be up-regulated in prostate cancer tissues and cell lines (183-185). They sponged miRs-1253, -497-5p and -330-5p, respectively, resulting in up-regulation of NRBP1 (186). Down-regulation of each of these circRNAs inhibited proliferation, migration, invasion, and EMT of prostate cancer cells *in vitro*, whereas apoptosis was stimulated. In nude mice, down-regulation of these circRNAs inhibited growth of PC3 and DU145 prostate cancer cells after SQ implantation

(183-185). NRBP1 is a pseudokinase that functions as a multidomain adaptor protein, which is ubiquitously expressed and contains two nuclear receptor binding motifs, a putative interaction site for SH2-containing proteins, a kinase-like domain, a bipartite nuclear localization signal, and three sequences rich in glutamic acid, serine, proline, and threonine (PEST) (186). NRBP1, a 535 aa protein, is involved in mediating steroid, thyroid hormone, and vitamin-induced signaling pathways. NRBP1 has different functions in different types of cancers. In breast cancer, NRBP1 is down-regulated and inhibits proliferation through the WNT/β-catenin signaling pathway (187). In triple-negative breast cancer (TNBC), NRBP1 activates RAC1/CDC42 oncogenic signaling (188). In prostate cancer patients, NRBP1 is highly expressed and associated with increased cell proliferation and poor clinical outcomes (189). NRBP1 might be an interesting new target for the treatment of prostate cancer; however, the signaling pathways activated by NRBP1 have to be resolved in the context of target validation efforts.

Circ100146 up-regulates thyroid hormone-receptor interacting protein 13 (TRIP13). Circ100146 (Figure 5) was up-regulated in prostate cancer and its down-regulation inhibited proliferation, migration, and invasion of 22Rv1 and DU145 cells *in vitro* (190). It sponged miR-615-5p and its down-regulation inhibited growth of 22Rv1 cells in nude mice after SQ implantation by up-regulation of TRIP13 (190). TRIP13 interacts with thyroid- and retinoid receptor, but not with glucocorticoid receptor (191). TRIP13 binds to transcriptional intermediary factor IB (TFIB), a central component of the complex of proteins necessary for transcriptional elongation (192). TRIP13 functions as an ATPase associated with diverse cellular activities (AAA+) and is involved in mitotic processes, spindle assembly checkpoint and DNA repair and may account for chromosomal instability (193). Amplification of TRIP13 has been observed in several types of cancer (193). It consists of 432 amino acids and harbors a N-terminal AAA+ substrate recognition region, which contains an ATP binding site (193). TRIP13 is a predictor of poor prognosis in prostate cancer patients and mediates proliferation, migration, and invasion of prostate cancer cells (194). Further delineation of the TRIP13-mediated molecular interactions and identification of the pathways induced by TRIP13 will be necessary for further target validation in prostate cancer.

Circular RNAs Affecting Ubiquitination

Circ RNA lysine demethylase 4A (circKDM4A) up-regulates cullin 4B (cul4B). CircKDM4A (Figure 5) was up-regulated in serum exosomes from prostate cancer patients compared to exosomes from healthy volunteers (195). CircKDM4A promoted proliferation, migration, invasion, and inhibited apoptosis of prostate cancer cells. In nude mice, silencing of circKDM4A inhibited tumor growth of prostate cancer xenografts. Circ KDM4A sponged miR-339-3p and induced cul4B (195). The latter acts as a scaffold of the cul4B-ring E3 ligase complex, which is over-expressed in many types of tumors, regulates proteolysis, and inhibits expression of tumor suppressor genes (196). In prostate cancer, cul4B has been shown to activate the PI3K/AKT/mTOR pathway (197, 198).

Circ plant homeodomain finger protein 16 (circPHF16) up-regulates ring finger protein 128 (RNF128). CircPHF16 (Figure 5) was down-regulated in prostate cancer tissues compared to corresponding normal tissues (199). In transwell and wound-healing assays, circPHF16 inhibited migration and invasion of DU145 and PC3 cells. CircPHF16 decreased metastasis of PC3 cells after tail-vein injection into nude mice (199). CircPHF16 sponged miR-581, increasing RNF128, which inhibited WNT/β-catenin signaling and EMT by targeting β-catenin (199). It has been shown that down-regulation of RNF128 activates WNT/β-catenin signaling and EMT in melanoma (200). In colorectal cancer (CRC) and hepatocellular carcinoma (HCC), RNF128 suppresses PI3K/AKT, WNT/β-catenin, and EGFR/mitogen activated kinase kinase (MEK)/ERK pathways (201, 202).

Circ midline 1 (circMID1) up-regulates MID1. CircMID1 (Figure 5) was highly expressed in prostate cancer tissues compared to benign prostate hyperplasia tissues, and in CRPC compared to AR-dependent prostate cancer (203). PC3 cells treated with exosomes derived from myeloid-derived suppressor cells up-regulated circMID1. circMID1 promoted proliferation, migration, and progression to CRPC *in vitro* and in nude mice. CircMID1 sponged miR-506-3p and up-regulated MID1 (203). The latter is involved in the microtubule-associated protein complex and functions as an E3-ubiquitin ligase. It is part of the tripartite motif (TRIM) subfamily of RING containing proteins and is also known as TRIM18 (204). It has been shown that MID1 is up-regulated during androgen-deprivation therapy and enhanced AKT, NFκB, and hedgehog (Hh) signaling, promoting castration resistance (205, 206).

Circ006156 blocks ubiquitinylation of S100 protein A9 (S100A9). Low levels of circ 006156 (Figure 5) were detected in prostate cancer tissues and cell lines (207). Circ006156 suppressed migration and invasion of DU145 and PC3 cells *in vitro* and inhibited experimental metastasis of PC3 cells to the lungs in nude mice due to up-regulation of S100A9. Circ006156 bound to S100A9 and inhibited its ubiquitinylation (207). It has been shown that S100A9 promotes growth of prostate cancer invasion by activating TLR4/NFκB/integrin β1/focal adhesion kinase (FAK) signaling (208). Also, S100A9 has been reported as a potential diagnostic marker for early prostate cancer, as it can distinguish between prostate cancer and benign hyperplasia, because serum levels of S100A9 are increased in prostate cancer patients (209).

Circular RNAs Affecting Metabolism

Circ phosphofructose kinase platelet (circPFKP) up-regulates inosine-5'-monophosphate dehydrogenase 2 (IMPDH2). CircPFKP (Figure 6) was increased in prostate cancer tissues compared with adjacent non-cancerous prostate tissues and expression correlated with tumor stage (210). It promoted proliferation of prostate cancer cell *in vitro* and in nude mice after SQ implantation. CircPFKP interacted with IMPDH2 and mediated biogenesis of GTP (210, 211). IMPDH2 was identified as a marker for aggressive and advanced prostate cancer (212). Silencing of IMPDH2 reduces prostate cancer cell proliferation (213). In prostate cancer patients, enhanced expression of IMPDH2 has been shown to promote metastasis (214).

Circ pyruvate dehydrogenase complex component X (circPDHX) up-regulates acetyl-CoA synthetase long chain family member 1 (ACSL1). Circ PDHX (Figure 6) was up-regulated in prostate cancer tissues and its inhibition attenuated prostate cancer cell proliferation, migration, fatty acid metabolism, increased apoptosis, and repressed tumor growth in nude mice. It sponged miR-497-5p and up-regulated ACSL1 (215). ACSL1 is part of an enzyme family, which is commonly de-regulated in cancer and is associated with poor survival (216, 217). All iso-enzymes convert free long-chain fatty acids into fatty acid acyl-CoA esters and thereby play a role in lipid biosynthesis and fatty acid degradation. They promote ungoverned cell growth, facilitate tumor invasion, and inhibit apoptosis (216, 218). ACSL1 has been shown to promote prostate cancer progression by increasing lipogenesis and fatty acid β-oxidation (218, 219).

Circ M6A RNA binding motif 33 (circ M6A RBM33) up-regulates pyruvate dehydrogenase, subunit α (PDHA1). Expression of circ M6A RBM33 (Figure 6) predicted poor prognosis in prostate cancer patients (220). Silencing of circ M6A RBM33 inhibited proliferation and invasion of 22Rv1 and DU145 cells *in vitro* and decreased tumor growth of corresponding xenografts in nude mice. Depletion of circ M6A RBM33 increased sensitivity to AR inhibitors ENZ and darolutamide. Circ M6A RBM33 interacted with fragile mental retardation protein 1 (FMR1), which stabilized PDHA1 (220). FMR1 is an RNA binding protein that mediates stabilization of mRNA and enhances translation (221, 222). PDHA1 is involved in

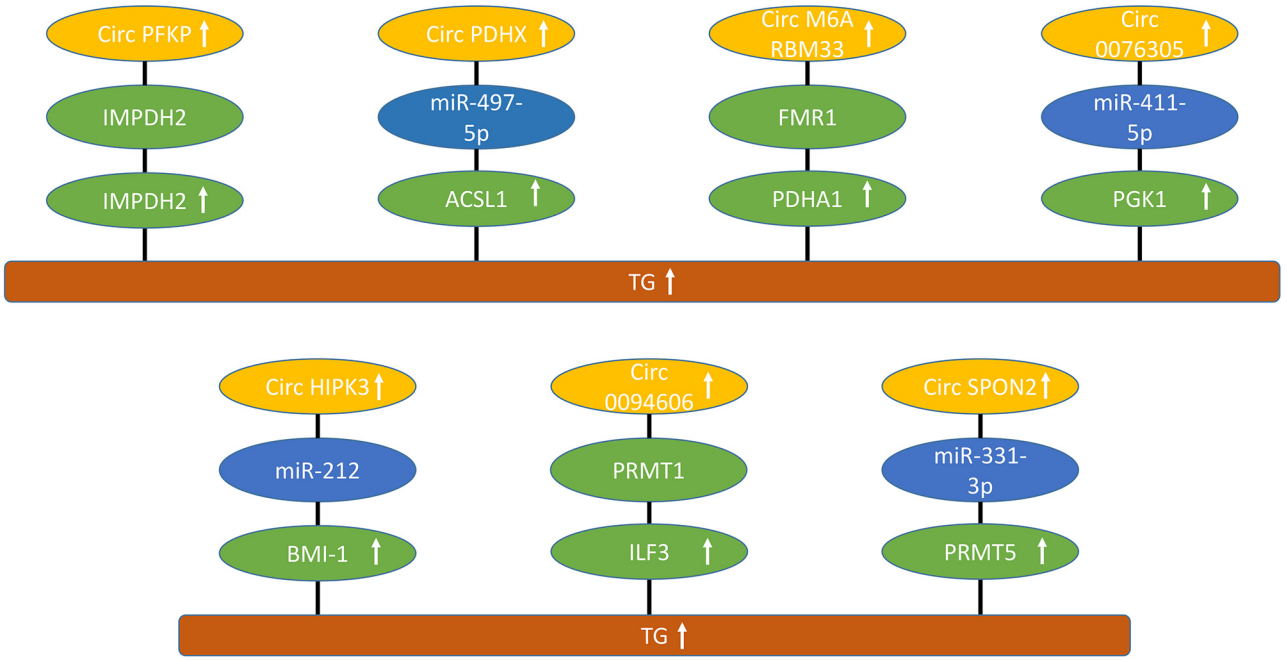

Figure 6. *Circular RNAs targeting prostate cancer-related components of metabolism and epigenetic modification with efficacy in preclinical in vivo models. First line: specifies circRNA; second line: indicates miRs or proteins interacting with corresponding circRNA; third line: highlights de-regulated targets; fourth line: indicates impact on tumor growth and metastasis. Upward arrows indicate up-regulation, downward arrows indicate down-regulation.ACSL1: Acetyl-CoA-synthase long chain family member 1; BMI-1: polycomb complex protein 1; circHIPK3: circ homeodomain interacting protein kinase 3; circPDHX: circ pyruvate dehydrogenase complex component X; circPFKP: circ phosphofructo-kinase platelet; circ M6A RBM33: circ M6B RNA binding motif 33; circSPON2: circ spondin 2; FMR1: fragile mental retardation protein 1; ILF3: interleukin enhancer binding factor 3; IMPDH2: inosine-5'- monophosphate dehydrogenase 2; miR: micro RNA; PDHA1: pyruvate dehydrogenase A1, subunit α; PGK1: phosphoglycerate kinase 1; PRMT5: protein methyltransferase 5; TG: tumor growth.*

mitochondrial respiration, pyruvate oxidation, and glycolysis (223, 224).

Circ0076305 up-regulates phosphoglycerate kinase 1 (PGK1). Circ0076305 (Figure 6) was highly expressed in prostate cancer tissues and its silencing triggered cell growth, migration, glycolysis, and induced apoptosis in prostate cancer. Interference with circ0076305 inhibited prostate cancer xenografts in nude mice. Circ0076305 sponged miR-411-5p and up-regulated PGK1 (225). PGK1 is a metabolic enzyme that is associated with poor prognosis, tumor growth, migration, and treatment resistance through phosphorylation of substrates (226, 227). PGK1 facilitates prostate cancer progression (226), metastasis (228) and prostate cancer induced bone formation (229).

Circular RNAs Affecting Epigenetic Modification

Circ homeodomain interacting protein kinase 3 (circHIPK3) up-regulates polycomb complex protein BMI-1. Exosomal circHIPK3 (Figure 6) was increased in the serum of prostate cancer patients (230). Exosomal circHIPK3 knockdown inhibited proliferation, migration, and invasion of 22Rv1 and DU145 cells *in vitro*. In nude mice, exosomal circ HIPK3 hampered growth of NB prostate cancer cells after SQ implantation. CircHIPK3 sponged miR-212 and up-regulated BMI-1 (230). The latter is part of the polycomb repressive complex 1 (PRC1), which inhibits transcription by trimethylation of histone H3 at lys 27 and subsequent inhibition of the RNA polymerase

pre-initiation complex by limiting the access of transcription factors to chromatin (230, 231). BMI-1 contains a helix-turn helix domain that binds to DNA, and a ring finger domain, which interacts with diverse substrates (230, 231). In prostate cancer, it has been shown that BMI-1 regulates stem cell renewal, malignant transformation, proliferation, migration, and chemo-resistance (232-234).

Circ0094606 up-regulates interleukin enhancer binding factor 3 (ILF3). Circ0094606 (Figure 6) promoted proliferation, migration and EMT of prostate cancer cells and increased their growth in nude mice (235). It binds to protein arginine methyltransferase 1 (PRMT1), which methylates ILF3, a protein which stabilizes interleukin 8 (IL8) mRNA, increases the expression of IL8, and induces polarization of macrophages to the tumorigenic M2 type (235). PRMTs are involved in the epigenetic regulation of gene expression by methylating histone proteins, but they also methylate non-histone proteins (236). ILF3 has been shown to act as an RNA binding protein and mediates cytokine induced angiogenesis (237). In prostate cancer, PMRT1 has been shown to regulate AR-mediated signaling (238). Furthermore, PRMT1 functions as an epigenetic driver of prostate cancer progression (239).

Circ spondin 2 (circSPON2) up-regulates protein methyltransferase 5 (PRMT5). CircSPON2 (Figure 6) was up-regulated in prostate cancer patients and promoted proliferation of DU145 and PC3 cells *in vitro* and stimulated growth of PC3 xenografts in nude mice (240). It sponged miR-331-3p and up-regulated PRMT5. PRMT5is up-regulated in prostate cancer and correlated with poor progression-free survival (240). It repressed expression of calcium/calmodulin dependent protein kinase II inhibitor 1 (CAMK2N1) (240, 241). PRMT5 inhibits the transcription of tumor suppressor genes by symmetric methylation of histone 3 at lys8, and histone 4 at lys 3 (13). CAMK2N1 functions as a suppressor of prostate cancer by inhibition of AR-dependent transcription (242). Furthermore, it has been shown that down-regulation of CAMK2N1 due to DNA methylation promotes progression of prostate cancer (243).

Circular RNAs Affecting Proteins of Other Categories

Circ sine oculis binding protein homolog (circSOBP) up-regulates myosin-light chain phosphatase1 (MYPT1). CircSOBP (Figure 7) was down-regulated in prostate cancer tissues and inhibited migration, invasion of DU145 and PC3 *in vitro* and experimental metastasis of DU145 cells in nude mice. It sponged miR-141-3p and up-regulated MYPT1 (244). The latter inhibited phospho-myosin light chain 2 (pMLC2), a mediator of invasion and metastasis (245). Myosin represents a motor protein, which is involved in muscle contraction and ATP-dependent actin based motility together with tropomyosin and troponin (245). MYPT1 is serine-threonine specific phosphatase, which dephosphorylates the light chain of myosin, which consists of three subunits (246).

Circ0006404 up-regulates cofilin 2 (CFL2). Circ 0006404 (Figure 7) was aberrantly up-regulated in prostate cancer (247). Interference with circ006404 inhibited proliferation and invasion of DU145 and LNCaP-AI cells, induced apoptosis *in vitro* and decreased tumor growth of DU145 xenografts in nude mice. Circ0006404 sponged miR-1299 and up-regulated CFL2, a protein involved in actin depolymerization (247, 248). CFL2 drives the cell invasive and metastatic properties of TGFβ in prostate cancer (249). Over-expression of its paralog, CFL1, correlates with aggressiveness in prostate cancer (250).

Circ0004296 binds to eucaryotic translation initiation factor 4A (EIF4A). Circ0004296 (Figure 7) was decreased in prostate cancer tissues, the blood and urine in comparison to corresponding samples derived from healthy donors (251). It inhibited proliferation, invasion, migration, and EMT of DU145 and PC3 cells *in vitro*. Inhibition of circ00044296 decreased tumor growth after SQ and orthotopic implantation in nude mice as well as metastasis

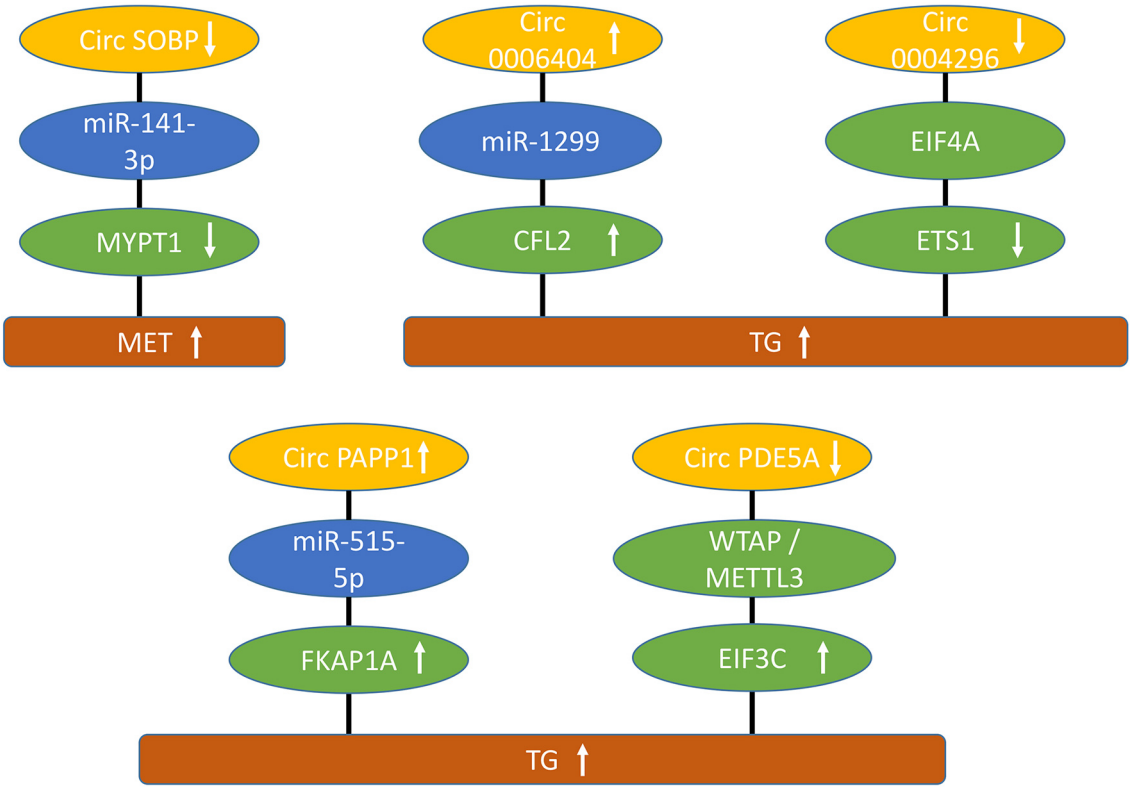

Figure 7. *Circular RNAs targeting prostate cancer-related components of other categories with efficacy in preclinical in vivo models. First line: specifies circRNA; second line: indicates miRs or proteins interacting with corresponding circRNA; third line: highlights de-regulated targets; fourth line: indicates impact on tumor growth and metastasis. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. CFL2: Cofilin 2; circPAPP1: circ pappalysin 1; circPDE5A: circ phosphodiesterase 5A; circSOBP: circ sine oculis binding protein homolog; FKAP1A: FKAP prolylisomerase 1A; EIF3C: eukaryotic initiation factor 3C; EIF4A: eucaryotic initiation factor 4A; ETS1: transcription factor ETS1; MET: metastasis; METTL3: M6-adenosin-methyltransferase 3; miR: micro RNA; MYPT1: myosin-light chain phosphatase 1; TG: tumor growth; WTAP: WT1 associated protein splicing regulator.*

to the lungs after tail vein injection. Circ 0004296 bound to EIF4A and inhibited nuclear export of transcription factor ETS1 mRNA (251). EIF4A, a member of the DEAD-box family of proteins was shown to be involved in oncogenesis as a mediator of proliferation and cell cycle progression (252, 253). In addition, EIF4A can facilitate nucleo-cytoplasmic transport (254). ETS1 induces TGFβ signaling and promotes EMT in prostate cancer (255). ETS1 is also increased in advanced prostate cancer and induces the CRPC phenotype (256).

Circ pappalysin 1 (circPAPP1) up-regulates FKAP prolylisomerase 1A (FKAP1A). CircPAPP1 (Figure 7) was over-expressed in prostate cancer and its knockdown inhibited cell viability, proliferation, and glycolysis, while restricting tumor growth of prostate cancer xenografts in nude mice (257). CircPAPP1 sequestered miR-515-5p and up-regulated FKAP1A, a member of the FK506 binding proteins (257). These are multifunctional proteins that are involved in mTOR/AKT signaling and the modification of chromatin structure due to their isomerase activity (258, 259). FKAPs can act as oncogenes as well as tumor suppressors in a context-dependent manner (258, 259). FKAP1A was shown to act as an oncogene in prostate cancer (260).

Circ phosphodiesterase 5A (circPDE5A) inhibits eucaryotic initiation factor 3C (EIF3C). CircPDE5A (Figure 7) was down-regulated in prostate cancer tissues compared to adjacent normal tissues (261). Over-expression of circPDE5A in C4-B and 22Rv-1 cells inhibited migration and invasion *in vitro*. 22Rv-1 cells transfected with circPDE5A led to decreased lung metastasis in an experimental metastasis model in nude mice. CircPDE5A formed a complex with WT1 associated protein splicing regulator (WTAP) and blocked N6A modification of EIF3C mRNA leading to disruption of its translation and inhibition of MAPK signaling (261). It has been shown that WTAP exerts N6A methylation by binding to N6-methyltransferase 3 (METTL3) (262). EIF3C activates PI3K, AKT, NFκB, and c-MYC in PC3 prostate cancer cells (263). In addition, it has been demonstrated that N6A modification of mRNAs contributes to progression of prostate cancer (152, 264).

Technical and Disease-related Issues

Nucleic acid (NA)-related therapeutic agents can be categorized into ASO (12-30 nts), siRNAs (21-23 nts), miRs (20-24 nts), small activating RNAs (21 nts), RNA aptamers (20-100 nts), and CRISPR-CAS based agents using guide RNA (265). Corresponding agents have been approved for indications such as transerythrin-mediated amyloidosis, Duchenne muscular dystrophy, and hypercholesterolemia (266). mRNA-based agents have received great attention for vaccination against viruses and cancer (266). Regarding tackling of circRNAs in cancer with ASO, siRNA, or CRISPR-CAS related agents, several issues have to be addressed and optimized: stability, off-targets effects, immunogenicity, as well as pharmaco-kinetic and pharmaco-dynamic properties (267, 268). Polymer- or lipid-based nano-particles and also inorganic-based delivery vehicles have contributed to delivery of NA-related agents (269). Liver delivery through the asialoglycoprotein receptor, targeting of the lungs by varying the composition of the lipids, and targeting of the blood-brain barrier are examples of recent achievements (270). Also, homing of different cell-types with designated peptides identified by phage-display related approaches have great potential with respect to delivery issues (271). The most important topic in the prostate cancer field is the treatment of castration-resistant and metastatic disease. Molecular mechanisms of resistance involve AR amplification, AR mutations, mutations in co-activators/co-repressors, androgen-independent AR activation, and intra-tumoral and alternative androgen production (272). Several internalizing receptors are potential targets for treatment of advanced prostate cancer such as: prostate-specific membrane antigen (PSMA), trophoblast surface antigen 2 (TROP2), small transmembrane epithelial antigen of the prostate 1 (STEAP1), tissue factor (TF), delta like protein 3 (DLL3), HER2, and B7 homolog 3 (B7H3) (8).

Concluding Remarks

We identified 49 de-regulated circRNAs with efficacy in preclinical prostate cancer-related *in vivo* models. These circRNAs belong to the following categories: therapy-resistance (n=8), transmembrane and secreted (n=7), transcription factors (n=8), signaling (n=7), human antigen R (n=2), nuclear receptor binding (n=2), ubiquitination (n=4), metabolism (n=4), epigenetics (n=3), and other functions (n=5). Forty of these circRNAs exert their functions by binding to miRs, while nine bind to proteins and mediate functions such as ubiquitination, formation of scaffolding complexes and mRNA-stabilization, -modification and -transport. From a clinical perspective, circRNAs and their corresponding targets associated with treatment resistance, CRPC, and metastasis are of particular importance. Notable findings include circXIAP and circSFBT2, which confer paclitaxel (PTX) resistance by targeting TPD52 and TRIB1, respectively. Similarly, circZNF609 and circZEB1, associated with radiation resistance, target HK2 and ZEB1, respectively (Figure 1). CircRNA17 which is involved in ENZ-R by targeting ARV7 has been identified as an important regulator of CRPC (Figure 1). In the category of CRPC-related circRNAs, circ0092339 was identified as an

inducer of c-MYC (Figure 3), and circMID1 (Figure 5) as an up-regulator of the ubiquitination enzyme MID1. Furthermore, nine circRNAs affect tumor growth and metastasis, or metastasis only. The up-regulated circRNAs of this category are circSMARCC (CCL6) (Figure 2), circ003258 (ARHGEF) (Figure 4), circMBOAT2 (mTOR) (Figure 4), and circFMN2 (KLF2, RNF128) (Figure 5). The down-regulated circRNAs include circ EXOC6B (AKAP12) (Figure 5), circPHF16 (RNF128) (Figure 5), circ006156 (S100A9) (Figure 5), circSOBP (MYPT1) (Figure 7) and circPDE5A (EIF3C) (Figure 7). The ranking of the identified circRNAs and their corresponding targets for the treatment of prostate cancer will require further validation experiments.

Conflicts of Interest

FB is and UHW was an employee of Roche.

Authors' Contributions

FB and UHW equally contributed to all aspects of the paper.

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